

PRACTICE OF MEDICINE

VOLUME I

PRACTICE OF MEDICINE

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VOLUME I

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FOREWORD

At the beginning of a work of this kind, it is perhaps timely and appropriate to consider some of the effects of the recent war upon medicine and its future.

“War begets Poverty—Poverty Peace,
Peace begets Riches—Fate will not cease,
Riches beget Pride—Pride is War's ground,
War begets Poverty, and so the world goes round.”

So runs an old saw, which seems to explore the causes of wars pretty thoroughly. Whatever its causes, the initial impact of the European war was as sudden and unaccountable as the great epidemic of influenza which attended its close and which has been relatively more destructive. In both instances, it seemed, at the start, as if the resources of Science had been brought to a standstill. The medical profession found itself face to face with new problems which taxed its ingenuity to the uttermost. But, in nearly every case, difficulties were promptly met and a solution found.

The first great problem was that of organization and team-work. In America alone, nearly 35,000 physicians were in uniform for the first time. They had to deal with such problems as the relation between the tempo of evacuation of the wounded and the rate of wound-healing, the examination of recruits, the service of medical supplies and sanitation, the management of military hospitals and hospital areas of vast capacity. At the front, one of the new functions of the Medical Corps was that of a human salvage corps, responsible not only for the care of the healthy and the disabled, but also for the eventual return of the greatest possible number of sick and wounded men to the trenches. Base Hospital practice and sanitation were conducted on a grand scale. From this experience, the practitioner from civil life learned much that is new about the organization of hospital work, the standardizing of medical practice, and community medicine in general. The profession everywhere has learned to think in larger terms.

Terrible and destructive as this war has been, yet on the medical side, compensations and benefits have accrued from it. The front has been a great outdoor school for sanitarians, surgeons, internists, neurologists and physiologists. We now know more about the various war neuroses, disorders of the peripheral nerves, the “effort syndrome” and other functional cardiac disturbances, trench nephritis, trench fever, “five-day fever,” the toxic and parasitic jaundices, the different pneumonias, the pathological effects of gassing, the psychology of soldiers,

the physiology of air-men, wound-infection, wound-shock, wound-treatment and reconstructive surgery. Typhus and the typhoidal diseases, the dysenteries, measles, mumps, meningitis, influenza, and other camp infections have been checked and finally suppressed. The dreadful pandemic which is still raging has slain more than have bullets and explosive shells. As the old proverbs tell, famine, disease and war usually go together. Much has been learned about food economics, food inspection, the effects of artificial or synthetic foods, the metabolism of starvation and the deficiency diseases. Infant welfare, the most unmilitary of subjects, has received a new impetus from this war. Its recent administration in France has been largely military, "under the shadow of swords." The war has evolved at least one new surgical principle, that of the excision of devitalized tissue in gunshot wounds. The new antiseptics devised by Dakin and Carrel are now to be tried out in civil practice. In the management of venereal diseases, we have learned the importance of the ethical side, the development of clean manhood, in making men "fit to fight."

One curious effect of war-time excitement and war-fatigue is the notion, now springing up in different countries, that medicine is in a chaotic state, at the end of its tether, necessitating a revision of basic principles. Englishmen are harking back to English medicine, Frenchmen to French medicine, and Germans to German medicine. Sir Clifford Allbutt, one of the veterans of our profession, declares, however, that the revolutionary changes of the last half decade have brought about a "new birth of medicine," that the close of the war is "the greatest moment in the history of medicine." The greater medicine of our time is experimental and preventive. Nearly all branches of medicine have advanced from the stationary or descriptive stage to the "dynamic" or experimental stage, in which laboratory medicine is applied to the prevention of disease. If you cannot reproduce a disease experimentally, you can seldom prevent it, or even treat it. Through the newer physiology of the nervous system, the digestive organs, the ductless glands, even anatomy, Allbutt says, has ceased to be static and has become dynamic. The physical principles of absorption, adsorption, osmosis, liquid films and surface tension are directly applied in physiology and pathology. The chemistry of enzymes, proteins, amino-acids, and carbohydrates, colloids, hormones and internal secretions, vitamins and synthetic foods, and of toxins, antitoxins and sera, is applied to the treatment and prevention of disease. Parasitology has given us the means of preventing malarial fever, yellow fever, hookworm infection, typhus fever and many tropical infections. Laboratory chemistry has devised new remedies for these parasitic diseases. Comparative pathology is throwing new light on human pathology. Of the gouty diathesis, Allbutt inquires: "Is a gouty man a kind of bird?" Some diseases, he says, are better studied in animals, some in plants. Experimental medicine and clinical medicine must fertilize each other henceforth. The bedside doctor and the laboratory investigator are now mutually dependent. The different sciences are and will be dependent upon one another. In

this matter of coöperation and coördination, much can be learned from the recent experiences of the profession in military medicine, which has given the doctor an opportunity to deal with his subject on a larger scale than ever before.

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PREFACE

It must be self-evident to all, especially those actively engaged in the practice or study of medicine, that new and important chapters are constantly being added, while many of the previously accepted ideas must be modified or entirely abandoned.

The history of medicine reveals constant changes with periods of marked progress. Comparatively, no era in the past can by any means equal the present in the rapid progress which is being made in true scientific medicine. This has been made possible by the achievements in the collateral branches, by the many new and applied clinico-laboratory methods, the introduction of various instruments of precision, the admirable modern clinical laboratories with the scores of earnest, sincere and determined workers, inspired with the spirit of original investigation.

Truly, the impossibilities or the day-dreams of yesterday have become the demonstrated and accepted facts of to-day. In addition to this marvelous progress, the present is equally remarkable for the varied and diversified activities in the various fields of medicine, each carried on in some locality most favorable to the growth of science by some particularly qualified individual or group of workers.

To keep informed of the numerous and ever-changing additions to medical knowledge is no easy task. A thorough review of the voluminous literature is impossible. Rejuvenating a library by frequent new editions has been tried and found wanting in more ways than one. To obviate this unnecessary expense and to furnish a means of ready reference to the most recent literature, an abstract service as a supplement to the present work has been adopted.

While following an etiologic basis, as far as possible, in the classification of the diseases, each article is written with the predominating idea of presenting the most important clinical manifestations, physical signs and means of diagnosis, with the appropriate and accepted treatment. This must be a source of satisfaction to the clinician and the busy practitioner.

The present work was undertaken, and well under way, before our country entered the late war. As soon as war was declared all activities were suspended as a patriotic duty. With cessation of hostilities and the return of the many contributors from active service, work was resumed with an increased vigor.

The task imposed upon the editor has been most congenial and profitable, made so by the hearty coöperation of contributors and publishers.

Public acknowledgment is made, while any adequate expression of appreciation is impossible. Sincere thanks are due the various contributors, the publishers, Geo. A. Wilson, M.D., managing editor, proof readers, indexer and others who have helped to bring this work to completion.

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CONTENTS

VOLUME I

SECTION I: GENERAL SUBJECTS

CHAPTER	PAGE
I. HISTORY OF ANCIENT MEDICINE	1
BY MAX KAHN	
II. HISTORY OF MEDICINE DURING THE MIDDLE AGES	15
BY MAX KAHN	
III. HISTORY OF MEDICINE DURING THE SIXTEENTH AND SEVENTEENTH CENTURIES	29
BY MAX KAHN	
IV. HISTORY OF EIGHTEENTH CENTURY MEDICINE	49
BY C. W. G. ROHRER	
Anatomy and Physiology	50
Embryology and Comparative Anatomy	56
Chemistry, General and Physiological	57
Pathology and Bacteriology	58
Materia Medica and Therapeutics	62
The Practice of Medicine	66
Surgery, General and Operative	72
Gynecology and Obstetrics	73
Hygiene and Preventive Medicine	74
The Diseases of the Eye and Ear	77
V. HISTORY OF MODERN MEDICINE	81
BY MAX KAHN	
VI. HYPERSENSITIVENESS	107
BY ARTHUR F. COCA	
Definition	107
Classification of the Phenomena of Hypersensitiveness	108
Anaphylaxis	110
Agents and Modes of Anaphylactic Sensitization	110
Exciting Agents of Anaphylaxis (Anaphylactogens)	110
Active Sensitization	117
Passive Sensitization	118
The Symptoms and Pathology of Anaphylaxis	124
Acute Anaphylactic Shock in the Guinea Pig	124
Acute Anaphylactic Shock in the Rabbit	125
Acute Anaphylactic Shock in the Dog	127
Summary of Acute Anaphylactic Shock	129

CHAPTER	PAGE
Protracted Anaphylactic Shock in the Guinea Pig	130
Protracted Anaphylactic Shock in the Rabbit	131
Protracted Anaphylactic Shock in the Dog	131
Summary of the Pathology of Anaphylactic Shock	133
Anaphylaxis in Human Beings	134
Local Anaphylaxis	136
Antianaphylaxis	138
Non-specific Antianaphylaxis	138
Specific Antianaphylaxis	138
Antisensitization	142
Theories of the Mechanism of Anaphylactic Shock	143
Humoral Theories	144
Cellular Theory	150
Physical Theory	153
Allergy	154
Definition	154
General Allergic Symptoms	154
Drug Allergy	156
Serum Allergy	162
Hay-fever	179
Tuberculin Sensitiveness	185
Tuberculin Allergy	190
Toxin Hypersensitiveness	191
VII. INFECTION AND IMMUNITY	199
By HERBERT K. DETWEILER	
Infection	199
Phenomena of Infection	199
The Path of Infection	202
The Problem of Virulence	207
Toxins	210
Method of Action of Bacterial Poisons	213
Immunity	214
Natural Immunity	214
Acquired Immunity	230
Toxin and Antitoxin	237
The Nature of the Toxin-antitoxin Reaction	238
The Production of Antitoxin for Therapeutic Use	244
Agglutinins and Precipitins	246
Agglutinins	246
Precipitins	254
Phagocytosis and the Opsonic Index	259
Phagocytosis	259
Opsonins	260
The Opsonic Index	262
Practical Value of the Opsonic Index	265
Hemolysins, Bacteriolysins, and Other Cytotoxic Substances	267
Phenomena of Lysis	267
The Nature of the Complement	272
Bordet-Gengou Phenomenon of Complement-fixation	274
Practical Applications of the Complement-fixation Phenomenon: The Wassermann Reaction	276
VIII. FOCAL INFECTIONS	303
By JOSEPH S. EVANS	
Introductory	303
Defenses of the Body against Bacterial Invasion	304

CONTENTS

xxxix

CHAPTER	PAGE
Localization of Invading Bacteria	307
Primary Focalization	308
Secondary Focalization	314
Acute and Chronic Diseases Secondary to Focal Infections	332
Heart and Pericardium	334
Serous Membranes	336
Joints and Bursæ	337
Skin Manifestations	343
Acute and Chronic Infections of the Gastro-intestinal Tract	344
Eye Infections	348
Thyroid Gland	349
Genito-urinary Tract	350
Infections of the Nervous System	351
Infections of Muscle Tissue	353
Infections of Bone Tissue	354
Toxic Effects of Focal Infections	355
Diagnosis of Focal Infections	356
Treatment	364
 IX. ORAL SEPSIS	377
By H. B. ANDERSON	
Definition	377
Historical Summary	378
Etiology	381
Pathology	386
Examination of the Mouth	391
Relation of Oral Sepsis to Systemic Disease	396
Diagnosis	411
Prognosis	413
Treatment	413
The Surgeon and Oral Infections	415
Insurance and Oral Sepsis	416
 X. PRACTICAL URINALYTIC METHODS AND THEIR SIGNIFICANCE	423
By MARTIN H. FISCHER	
Introduction	423
The Importance of Urinalysis	424
The Collection of Urine	424
The Preservation of the Urine	425
Physical Qualities of the Urine	426
Acidity Determinations	433
Titration Acidity	433
Hydrogen-Ion Acidity	435
Acetone Bodies (Acetone, Beta-oxybutric and Diacetic Acids)	440
Introduction	440
Abnormal Acids of the Urine	449
Mechanism of the Production of Acetone Bodies	442
Counteraction of Acetone Production	443
Tests for the Acetone Bodies	445
Reducing Substances in the Urine (Sugar)	445
Fehling's Test	445
Mechanism of the Production of Sugar in the Urine	447
Diabetes Mellitus	451
Proteins in the Urine (Albuminuria)	455
Qualitative Tests for Protein	455

CHAPTER	PAGE
Qualitative Estimations of Protein	456
Origin of Urinary Protein	457
The Albuminuria of "Nephritis"	459
Erroneous Deductions to Be Guarded against in Urinary Anal- yses in Nephritis	464
Introduction	465
The Technic for Microscopy in Urinalysis	466
Summary	469

XI. THE CEREBROSPINAL FLUID AND ITS RELATION TO HEALTH AND DISEASE 475

BY DAVID J. KALISKI

Historical Survey	475
Physiology of the Cerebrospinal Fluid	477
Mechanism of Secretion	477
Permeability of Choroid Plexus	478
Absorption of the Cerebrospinal Fluid; Factors Influencing Secretion; Pressure of the Cerebrospinal Fluid	479
Protection against Infection	485
Physical and Chemical Characteristics of the Cerebrospinal Fluid	487
Color	487
Specific Gravity	490
Reaction	490
Inorganic Constituents	491
Organic Constituents	491
Technic of Lumbar Puncture	494
Aseptic Precautions	498
Needles and Apparatus Necessary	498
Site of Puncture	500
The Puncture	501
Amount to Be Withdrawn	505
After-treatment	506
Lumbar Puncture under Anesthesia	507
Lumbar Puncture Headache	507
Methods of Examination of the Cerebrospinal Fluid	509
Tests for Protein (Globulin and Albumin)	509
Potassium Permanganate Reduction Test	511
Tests for Reducing Substance (Glucose)	512
Tests for Other Constituents	512
Cytological Examination of the Cerebrospinal Fluid	513
Bacteriological Examination of the Cerebrospinal Fluid	515
Serology of the Cerebrospinal Fluid	516
Colloidal Gold Test	519
Cerebrospinal Fluid in Syphilis of the Nervous System	523
Significance of Pathologic Cerebrospinal Fluid in Late Syphilis	524
Clinical Value of Biological Reactions	525
Relation of Secretion and Absorption of the Cerebrospinal Fluid to Intraspinal Therapy	528
Permeability of the Choroid Plexus and Meninges	529
Lumbar Puncture as a Therapeutic Procedure	531
The Meningitides: Description and Differentiation	533
Meningitis Sympathica	535
Acute Anterior Poliomyelitis	537
Trichinosis	537
The Cerebrospinal Fluid in Neurology and Psychiatry	538

CONTENTS

xli

CHAPTER	PAGE
XII. CASE HISTORY TAKING	551
BY ARTHUR BYFIELD	
General Considerations	551
Materials	561
The History Proper	572
Present Illness	572
Previous Illness	578
Family History	580
Personal Routine	582
Venereal History	585
Menstrual History	586
Symptoms Which May Be Noted by the Examiner While He Is Writing the History and before He Has Begun the Ex- amination Proper	587
Mental State	587
Mode of Approach	588
Facial Expression	588
Position in Bed	588
Relation of Appearance and Age	589
State of Nutrition	589
Skin and Mucous Membranes	590
Hair and Nails	590
Lymph-nodes	590
Vasomotor Disturbances	590
Cough and Expectoration	591
Breathing	591
The Voice and the Speech	591
The Eyes	591
The Ears	592
The Teeth	592
The Breathing and the Body Odor	592
The Extremities	592
The Abdomen	592
Edema	592
Visible Nervous Manifestations	592
INDEX	595

LIST OF ILLUSTRATIONS

VOLUME I

SECTION I: GENERAL SUBJECTS

CHAPTER IV

HISTORY OF EIGHTEENTH CENTURY MEDICINE

FIGURE	PAGE
1. William Hunter	51
2. Albrecht von Haller	55
3. Giovanni Battista Morgagni	59
4. William Cullen	63
5. Herman Boerhaave	67
6. Benjamin Rush	69
7. John Hunter	71
8. Edward Jenner	75

CHAPTER VII

INFECTION AND IMMUNITY

1. Ehrlich's side-chain theory, side-chain of the first order . . .	225
2. Ehrlich's side-chain theory, side-chain of the second order . . .	228
3. Ehrlich's side-chain theory, side-chain of the third order . . .	230
4. Agglutination of the corpuscles of the various groups . . .	250
5. Ehrlich's side-chain theory, showing composition of side-chain of the third order	268
6. Ehrlich's side-chain theory, showing combination of side-chain of third order with antigen and complement	270
7. Ehrlich's side-chain theory, side-chain of third order with antigen, before addition of complement	270
8. Chart showing Bordet-Wassermann test during treatment of syphilis (secondary)	298
9. Chart showing Bordet-Wassermann test during treatment of syphilis (secondary)	299
10. Chart showing Bordet-Wassermann test during treatment of syphilis (tertiary)	300

CHAPTER VIII

FOCAL INFECTIONS

1, A. Granuloma from root of tooth, showing dense fibrous wall surrounding the point of infection	312
1, B. Photomicrograph showing mass of streptococci from area of infection in granuloma from root of tooth	313

FIGURE		PAGE
2.	Chart showing position of various members of the streptococcus-pneumococcus group as regards virulence, sensitivity to oxygen, and reaction upon blood agar on isolation, and the probable position as regards transmutation of forms based on the experimental work of Rosenow	317
3.	Vertical transverse section of head cut in the region of the molar teeth, showing relation of nasal cavity and its accessory sinuses	322
4.	Roentgenogram of a chronic maxillary sinusitis, showing the antrum filled with granulation tissue	323
5.	Section of a tonsil which clinically appeared to be healthy, showing a small abscess	324
6, A-D.	Roentgenograms of a case of subacromial bursitis of twelve years' duration	340, 341

CHAPTER IX

ORAL SEPSIS

1.	Longitudinal section of decayed dentine, showing infection with rod-and-thread forms	382
2.	Decayed dentine, showing total liquefaction of the substance by bacteria	382
3.	Multiple plate	383
4.	Interglobular spaces filled with micrococci	383
5.	Periapical infection associated with retained instrument	385
6.	Periapical infection associated with crown, deep-seated cavity and pivot tooth	385
7.	Periapical infection associated with deep-seated cavity	385
8.	Periapical abscess surrounding vital tooth, with septic tooth anterior to it	385
9.	Periapical abscess of vital tooth	385
10.	Periapical abscess, pulp dead; results of trauma	385
11-17.	Periapical infection associated with improper root-canal filling	387
18-21.	Retained septic roots	389
22-26.	Pyorrhea alveolaris	390
27-35.	Periapical infection associated with crowned teeth	392
36-44.	Periapical infection associated with pivot tooth	393
45-47.	Marked periapical infection associated with systemic symptoms without external evidence of disease	395
48-49.	Extensive pyorrheal and apical infection of long standing in male patient, aged 63, with no systemic symptoms except recent lumbago	397
50-54.	Extensive oral infection, which produced multiplicity of systemic diseases	399
55.	Infection of deciduous tooth, with secondary infection of submaxillary lymph-nodes	400
56.	Unerupted supernumerary tooth pressing on adjacent posterior molar	412
57.	Impacted tooth showing infection and odontomata associated with epilepsy	412

CHAPTER XI

THE CEREBROSPINAL FLUID AND ITS RELATION TO HEALTH AND DISEASE

1.	Lumbar puncture: sitting position	495
2.	Lumbar puncture: recumbent position	496
3.	Lumbar puncture: recumbent position	497

LIST OF ILLUSTRATIONS

xlv

FIGURES

	PAGE
4. Apparatus for lumbar puncture and intraspinal therapy . . .	499
5. Lumbar puncture: introduction of the needle	500
6. Lumbar puncture: introduction of the needle	501
7. Lumbar puncture: pressure reading	502
8. Lumbar puncture: pressure reading; closer view	503
9. Lumbar puncture: withdrawal of fluid	504
10. Lumbar puncture: intraspinal injections by gravity method, showing apparatus in position	504
11. Lumbar puncture: intraspinal injection; another view . . .	505
12. Types of colloidal gold reaction	521

CHAPTER XII

CASE HISTORY TAKING

1. Card illustrating a poor method of recording the medical history and the data of the examination	553
2. Reverse of card shown in Fig. 1	554
3. A four-page history form, which, although rigid in some ways, possesses many of the points commended in the text	557-560
4. A four-page type of history sheet recommended by the au- thor	563-566
5. Examples of laboratory forms	568-569
6. An unsuitable form for recording blood examinations . . .	570
7. An unsuitable form for recording urinalyses	571
8. Illustration of the first method for developing the "Present Illness" of the patient	573
9. The same case history as in Figure 8, arranged according to the second method of developing the "Present Illness" . . .	575

PRACTICE OF MEDICINE

VOLUME I

SECTION I

GENERAL SUBJECTS

CHAPTER I

HISTORY OF ANCIENT MEDICINE

BY MAX KAHN, M.A., PH.D., M.D.

The search for the cause of things and events exists since the appearance of man on the face of the earth. The inability to explain things reasonably and convincingly induced the thinkers of ancient times to use their imaginative faculties. The ancient explainers of natural phenomena were the poets.

The continual strife with the elements, the dreadful toils and dangers of man's life, the inclemency of nature—were all attributed to a perverse divinity or demon, who delighted to inflict pain and misery upon brief-lived mortals. Such a divinity needed worship and sacrifice to propitiate him. Humanity began to fear the devil before they imagined the god. The "earthworms" created the gods of goodness to protect themselves against the spirit of evil which they had incarnated.

With fear began superstition, which is based upon fear and ignorance. The desire to know the mysterious future has given rise to a great deal of the world's store of credulity in the supernatural. The ancient philosopher who desired to divine the future by means of geometrical figures, the pretty maiden who counts the petals of the daisy or dandelion to learn whether her lover will be constant, and the man of affairs who allows the clairvoyant to pass on the lines of his hand—are the common examples in life of the vain endeavor to raise the curtain which hides what is to be. Living beings fear death—a rational fear. In order to prolong life, the body is to be kept healthy, illnesses are to be avoided, and, if disease does affect an individual, the sickness is to be cured. This is all rational. But illnesses are almost inevitable in man's life, and diseases are not always cured or curable. Instead of combating disease logically, men of all classes drew upon their imagination and devised various absurd means and methods of treating their ailments.

Coeval with the birth of superstition was the birth of magic. The charlatan, who could unscrupulously play upon the feelings of his igno-

rant audience, had quite a mighty following in every locality where human beings suffered and hoped. Religion and magic can flourish simultaneously in great amity. For example, the establishment of the Roman Church in England did not induce the old Anglo-Saxons to abandon their ancient rites and ceremonies. The inhabitants still clung to the mysterious lore of the Druids and were only able to attach themselves to the new belief by retaining quite a number of the heathen superstitions. Long after the coming of the Catholic missionaries to the British Isles, there thrived in "merrie England" hundreds of magicians who were feared even more than the holy fathers. For the ignorant person ever loves to compromise. He is never certain which god is the true god, and in order not to take chances, he sacrifices to more than one divinity, lest he be left in the lurch. Palmists, fortune tellers, necromancers, magicians, clairvoyants, are always secure of a very comfortable livelihood, if they do but settle in those centers where ignorance abounds. For, indeed, they seem all omnipotent to the credulous mind. They can predict the future; they can sell love-philters; they can cast evil spells upon our enemies; they can give us an amulet which we can wear and be forever protected against fearful maladies; they can grant good luck, and tell us how to avoid dangers and pitfalls.¹

In the ancient folk lore of all races, we find the history of the origin of medical therapeutics. For every evil invented by the devil, God has created a remedy. The cure was not always known, because the ingredients of the medicine were very numerous and varied. In order to obtain the remedy in its full potency, the portions that made up the various concoctions were to be in exactly proper portion, otherwise the medicament would prove useless. The numberless combinations possible were to be tried out, and those that proved beneficial were treasured. Certain localities did a roaring trade in the sale of the specific for which they were noted. In modern times the nostrum and patent medicine have replaced these Meccas of healing, and the descendants of the ancient sufferers and believers are now filling the coffers of quacks.

The medical art of yore was entirely practiced by the haggard old witch or gray-bearded magician, who lived in surroundings calculated to inspire awe in the hearts of their clients. Besides some all-beneficial drug mixture, they could also give (for a price) certain amulets to be worn, or suggest some mystic word-charm to be spoken to conjure away disease. "Abracadabra" chanted confidently the early Christians, "Hax Pax Max," the medieval wizard, "Ista Pista Sista," the Roman Cato—and all derived complete satisfaction seemingly from these powerful incantations.

The medicine of the ancient Chinese, Hindoos, Egyptians, Hebrews, Persians and other Asiatic and African races is chiefly described and discussed in their religious writings and ceremonies. The priests were the ancient physicians. Among the Hebrews the men who practiced the healing art were held in especial awe and reverence. "Honor the physician," writes Joshua, the son of Sirach, "with the honor due unto him, for the uses which ye may have of him; for the Most High cometh

healing, and he shall receive honor of the King. The skill of the physician shall lift up his head; and in the sight of great men he shall be in admiration. The Lord hath created medicines out of the earth, and he that is wise will not abhor them. . . . Then give place to the physician, for the Lord hath created him: let him not go from thee, for thou hast need of him."²

Just as science and art are international, so are ignorance and superstition. To examine the vacuum of learning among the ancients which has been called medicine, needs but to investigate the practices current in any one country, and remarkable duplications will be seen in every other country. Either the one God was the great healer, or there were special gods who particularly patronized the physicians and the sick. In Egypt, I-em-hotep, in Greece, Æsculapius, among other nationalities, other gods, were worshiped and propitiated by sacrifices. Temples were erected to these divinities and the sick and maimed came and prayed, and many went away cured. The priests chanted hymns, advised medicinal remedies, sold amulets and trumpeted forth the great ease with which their god healed. Some of the cures were remarkable: "A man who had only one eye was visited by the god during the night. The god applied ointment to the empty orbit. On awakening he found that he had two sound eyes. . . . The son of Hermione was blind in both eyes. A dog of the Temple licked them, and immediately he regained his sight. . . . Another man had no hair on his head. He prayed to the god to make it grow again. Æsculapius applied some ointment, and next morning there was a thick growth of hair."³ And the masses believed in all this hodge-podge just as the masses now believe in other hodge-podge. There arose several thinkers in the age of Pericles who did not give due credence to the wonders that the gods of their fathers were supposed to have worked. Whereat the mob, incited by the temple priests, felt outraged and persecuted and slew the sages. They condemned Anaxagoras to death; they cursed Euripides as a heretic; Æschylus escaped being stoned by reading his dramas to the courts; Socrates, true martyr, drank the cup of hemlock that his jailers gave him, and discussed wisdom while dying.

The history of European medicine begins with the Philosopher of Samos, Pythagoras, whose influence prevailed over the medical opinions of the time. He lived six centuries before Christ. A great traveler and a great student, his fame is almost legendary. He visited Egypt and India, and returned to Greece full of the mystical ideas held by the priests of these countries. He taught his pupils the doctrine of Metempsychosis, the prejudices against animal diet, the magical notions respecting the powers of numbers, and other fantastical doctrines of the orient. He investigated the structure of the body, reproduction and development, the functions of the senses and mental activity, as well as the treatment of the sick. Remarkable for that epoch, he denied the origin of life from decomposing matter, asserting the necessary existence of an embryo.⁴

Pythagoras, however, was a philosopher. He touched on medicine, simply because medicine is part of philosophy. To his younger contemporary, who may have also been his pupil, Alcmaeon of Crotona, is due the honor of being the first Greek writer on medicine. According to the concurrent testimony of Aristotle, Diogenes, Plutarch and Chalcidius, Alcmaeon was the first to dissect brutes in order to discover the internal structure of the animals. The theories and so-called facts which he promulgated are a peculiar blend of the remarkable and the ridiculous. Health was supposed to be dependent on the accurate adjustment of heat and dryness, coldness and humidity, bitterness and sweetness and other qualities, while sickness was due to a predominance of one quality. The cure of disease was, therefore, properly to determine what was lacking and to restore the balance by the addition of the missing quality. He believed that goats breathed through their ears; that hearing was due to the concave form of the ear; that the brain was the seat of the soul; that odors went through the nose to the brain; that sleep was due to the storage of blood in the larger vessels; that the head was the first part of the fetus formed so that it could take nourishment *in utero*. But he also knew that semen did not come from the spinal cord—this he proved by experiments on animals; that the brain was the central organ of intellectual activity; that the optic nerve existed.

The successors to Pythagoras were Philolaos and Empedocles, who modified somewhat the theories of their teacher. According to Philolaos, the causes of disease are due to a disturbance of the bile, blood and phlegm; one becomes predisposed to illness due to excess or lack of warmth, nourishment, etc.; inflammation is caused by excess of phlegm. He taught that there are three functions in man—the “human,” the “animal,” and the “vegetable.” He asserted that the “human” function is located in the brain; the “animal” element is in the heart; the “vegetable” element, growth, is in the navel.

Empedocles, a poet and philosopher of Agrigentum, a town of Sicily, taught that there were four elements in existence which possessed a soul: fire, air, water and earth, which in combination in varying quantities, produced different parts of the body. For example, blood was composed of four equal portions of the elements, whereas bones, on the contrary, were made up one-half of fire and one-quarter each of earth and water. His doctrine of force is important to mention. It appeared to him that two main forces ruled the world—love and hate. These alternately shape the construction, development and decay of all creations. During dissolution of matter, the liberated elements unite with their like in space; i.e., air to air, earth to earth. Certain of his theories, as handed down by Galen, seem to us not understandable. Take, for instance, his theory of respiration: “As soon as that humidity, of which there is a great store on the first formation of the fetus, begins to be diminished, the air insinuating itself through the pores of the body succeeds it; after this, the natural heat, by its tendency to make its escape, drives the air out; and when this natural heat enters the body

again the air follows it afresh. The former of these actions is called inspiration, and the latter expiration."

Neuberger has this to say of Empedocles: "He was physician, seer, priest and poet in one. Honored as a god by his contemporaries, his influence made itself felt throughout Hellas; his life, his deeds and his death being surrounded by a halo of myth. 'In a purple robe, gold-encircled, long hair framing his gloomy countenance, crowned with the priestly laurel, he traveled through the country districts of Sicily, surrounded by a host of worshipers of both sexes. Thousands, even tens of thousands, acclaimed him, prostrated themselves before him, and demanded of him favorable forecasts for the future no less than healing for all manner of disease.' He freed the town of Selinus from a devastating scourge by reclaiming the swampy land, and he assured his native town of Agrigentum favorable climatic conditions by blocking up a rift in a hill."

With the physician of Cos, Hippocrates, began medical theorization in Greece. The Father of Medicine introduced certain generalizations in his conceptions of disease causation, after due study and experience. "Theory is the flower, not the root of experience," was his motto. As Neuberger points out, what Socrates was to philosophy, Hippocrates was to medicine. "In both is embodied the reaction of practical reason against shallowness and theoretical excess. Both, in the midst of obscurity, morbid speculation and fruitless hypercriticism, stand for the golden mean in thought, leading to naked truth. Both, with a wise self-restraint, keep within the bounds of their respective domains, their activity centering around moral law and a highly idealized utilitarianism."

This celebrated physician was born in the Island of Cos, in the year 460 or 459 B. C. His father, also a physician, gave him his initial medical education. He traveled through the various Hellenic cities, practicing his art and making the acquaintance of the famous Greeks of his day. During his lifetime he was greatly honored by his fellowmen. Plato considered him equal in fame and ability to Polyelertos and Phidias. He was called "divine" by Galen, and the "father of medicine" by all who practice the Hippocratic Art.

He laid down the rule that "no disease comes from the gods, one more than another, each acknowledging its own manifest and natural cause." This is the divorce announcement of mystical practices and bedside observation, for though he had a reverence for the teachings of his professional ancestors, the I-em-hotep and Æsculapius of old, Hippocrates saw their crudities and wondered at their ignorance, and in this he was the scientific progenitor of Harvey and Pasteur and Lister.

In his therapeutics, Hippocrates taught that "natural powers are the healers of disease." He treated his patients by regulating their diet, prescribing baths and a change of climate, advising poultices, purgatives, venesection and diuretics, and eschewing to an extent remarkable for his age the ridiculous medicamentary mixtures used by his contemporaries.

He was especially acute in his bedside observations. He judged of the patient's state of health by the facies, posture, voice and excretions. It was his custom to examine the urine, feces, expectoration, sweat and pulse of his patients. Among his aphorisms for the cure of disease are the following: that contraries, or opposites, are a remedy for each other; that evacuation is a remedy for repletion, and repletion for depletion.⁵ He made experiments on the digestibility of food—the first physiological investigations recorded—and held the theory that “all parts of the body which are designed for a definite use are kept in health, and in the enjoyment of fair growth, and of long youth, by the fulfillment of that use, and by the appropriate exercise in the employment to which they are accustomed. But when diseased they grow ill, stunted and become prematurely old.”

In his ethical teachings he had an ennobling influence on the medical profession. These are his moral requirements of the Physician:

“Touching his state of mind, he must be heedful of the following: He must not only know how to be silent at the right time, but must lead a well-ordered life, for this adds much to his good repute. Let his disposition be that of a man of honor, and as such let him behave to all honorable men in a friendly and easy spirit. Precipitation and impetuosity are not liked even though they be of use. As to his bearing, let him wear an expression of sympathy, and not show vexation which would indicate presumption and misanthropy. Who on the other hand laughs readily, and is at all times merry, becomes a burden, whence this is particularly to be avoided.”

And what can be more noble and inspiring than the Oath of the Coan School which the young practitioner took, and which is now known as the Hippocratic Oath?

“With purity and with holiness will I pass my life and practice my art. Into whatever houses I enter, I will go into them for the benefit of the sick, and will abstain from every voluntary act of mischief and corruption; and further from the seduction of females and males, of freemen and slaves. Whatever in connection with my professional practice, or not in connection with it I see or hear, I will not divulge, as reckoning that all things should be kept secret. While I continue to keep this oath inviolate, may it be granted to me to enjoy life and the practice of my art, respected by all men at all times. But should I trespass and violate this Oath, may the reverse be my lot!”

The next great Greek to influence markedly the progress of science was Aristotle, who lived from 384 to 322 B. C. In his writings we find the fundamentals of natural history, and an epitome of Hellenic contribution to natural philosophy. During approximately the twenty centuries that followed him, his written word was law in the domain of science. Together with Galen, he swayed the medical opinions up to

the seventeenth century. Men refused to believe the evidence of their senses. If an observation did not agree with Aristotle, the observation was wrong, not Aristotle. Instead of taking the Stagyrice as a scientific authority whose observations may be corrected and whose theories may be improved, he became an authority on faith, whom it was heretical to contradict, with the result that ignorance triumphed. "Science and faith," said Hippocrates, "are two things: the first begets knowledge, the second ignorance."

Nevertheless, and in spite of the bad influence that he exerted during the middle ages—not at all due to his own fault, but due to the stagnant spirit of the times—Aristotle of Stagyrice was the greatest student of Nature in ancient history. Of recent times, men have been prone to underestimate his knowledge, because of his pernicious influence on his successors. Macfie writes that the Stagyrice owes his scientific reputation to his garrulity and to the ignorance of his audience. Hallam estimates his philosophical writings as a "barren tree that conceals its want of fruit by profusion of leaves." But there is something unfair in this opinion.

He was a pioneer in science. "I found," he writes, "no basis prepared, no models to copy. . . . Mine is the first step, and, therefore, a small one, though worked out with much thought and hard labor. It must be looked at as a first step, and judged with indulgence." It was not his blame if Christian theologians placed him on a divine pedestal, and consigned to the flames any one who ventured to deny certain of his theorems. As Roger Bacon (who barely escaped being condemned as a wizard for his experimental work) asserts, "Aristotle hath the same authority in philosophy that the Apostle Paul hath in divinity." To lower science to the level of a creed is to invite stagnation and ignorance.

Aristotle was the founder of systematic zoölogy. "His observations on structure and development, and his anticipation of the idea of organic evolution, are the ones upon which his great fame rests. . . . He knew that drone bees develop without previous fertilization of the eggs (by parthenogenesis) . . . that some sharks develop within the egg tube of the mother. . . . He had followed day by day the changes in the chick within the hen's egg. . . . In embryology, also, he anticipated Harvey in appreciating the true nature of development as a process of gradual building, and not as a mere expansion of a previously formed germ."⁶ In medicine, however, he reported many erroneous observations. He supposed the brain to be bloodless; that the liver, spleen and kidneys served merely as a support for the veins; that the arteries carried air; that the nerves originated in the heart which was the seat of the soul. These errors were held to be divine truths for many centuries.

After Hippocrates, the great progress made in medicine was in Alexandria. There, under the learning-loving Ptolemies, the doctors found favorable patronage, and could, therefore, pursue their studies of herbs and anatomy. Herophilus of Chalcedon (300 B. C.), pupil of Praxagoras and Chrisippus, was famous for his great knowledge of medicine

and for his surgical skill. It was he who discovered the torcular Herophili in the cranium, and he made much progress in anatomical terminology. He described the meninges, ventricles, blood sinuses and choroidal plexuses of the brain; he recognized the lacteals, gave the duodenum its name, and carefully described the liver. Herophilus was a commentator on the writings of Hippocrates, and he also wrote on diet, gymnastics, obstetrics and surgery.

Contemporary with him was Erasistratos, who died about 250 B. C. He was a student of Anatomy, having made many dissections of cadavers of human beings and animals, making special contributions to the knowledge of that time of the brain, heart, trachea, liver, intestines, etc. He considered the body, compounded of atoms, to be vivified by heat originating outside, not generated within. He thought the blood to be a conversion product of ingested food, which serves to build up the body.

But the Alexandrian School made more progress in theorizing than they did in practice, and this disgruntled the practically inclined, who, as Celsus says, were more interested in the treatment of disease than in its diagnosis or prognosis. A few of their phrases are very illuminative of their tenets: "The husbandman and the navigator are not trained by disputations but by practice. Diseases are not cured by talk, but by drugs. The important question is not who causes disease, but who dispels it." These dissatisfied practitioners established the so-called Empiric School, which reached the height of its influence during the life of Heracleides of Taras (about the first century B. C.). He was a pupil of Manteas, a famous surgeon of that time. Learned as he was in pharmacology, he was also noted for his surgical abilities. He made great progress in the treatment of fractures and dislocations, and he was especially famous for his herniotomy operations. He did not consider it below his dignity to cut for the stone, and, indeed, he improved the lithotomy operation.

With the decline of Greece and the development of the Roman power there was a continuous migration of Hellenic physicians to the City on the Tiber. The boorish Romans, untutored in the fine arts, could not appreciate the cultured Greeks. Cato, the philosopher, would not permit a Greek physician in his household, and, indeed, he wrote several epistles against allowing the Greeks to practice in Rome. It is true that on many occasions the foreign physicians, driven to it by poverty, aided certain wealthy patricians in their debauches and in their plots to poison their enemies. It is instructive to note the fate that befell Archagathos, a Greek immigrant in Rome. At first he was greatly honored and his skill and dexterity were so much praised that the Senate of Rome conferred on him the thanks of the city. But once in his large and lucrative practice he lost a patient, who died after an operation. The fickle mob forgot his great abilities, and in their rancor drove him from the city, confiscating his property (219 B. C.).

In Rome there flourished what was known as the Methodist School, founded by Themison, whose pupil, Thessalos of Tralles, was its greatest exponent. Thessalos was a contemporary of Nero. He was the son

of a weaver, and the greatest quack of his day. He very much restricted surgical interference in case of disease. He believed in practicing on the minds of his patients, and, truly, his prescriptions contained many harrowing ingredients.

According to the Methodist Doctrine, bodily ailments were arranged under three heads: the first comprising such as proceed from stricture; the second, those which arise from relaxation; and the third, those which assumed a mixed character. The science of medicine consisted wholly in the observance of a small number of rules, founded upon matters which are altogether evident. The treatment of disease should be directed in remedying the strictum or laxum by means of opposing therapeutic measures acting upon the whole body.

The teachings of Themison seem to have been held in no great respect by his contemporaries. Juvenal satirically refers to him in one of his verses:

"How many sick in one short autumn fell,
Let Themison, their ruthless slayer, tell."

Soranus, a native of Ephesus, and Meges of Sidon were two noteworthy followers of Themison.*

A. Cornelius Celsus (25 A. D.) was one of the greatest encyclopedists of ancient Rome. He so logically and clearly reviewed the history of medicine up to his time, that we owe to him much of the knowledge that we possess of ancient medicine. In his writings, "*De Medicina Libri Octo*," we have a complete résumé of the history of the healing art previous to him and during his time. It is written in elegant Latin, and its diction rivals Tacitus' history. Books 5 and 8 are devoted entirely to the art of the surgeon. In Book 4, Chapter 10, we find this oft-quoted statement: "*Notæ vero inflammationes sunt quattuor, rubor et tumor, cum calore et dolore.*"

Contemporary with Celsus, lived the younger Pliny (23-79 A. D.), whose respect for physicians was not very great. He loved to quote the tombstone epitaph, "He died by reason of the confusion of the doctors." In that famous book of his known as the "*Natural History*," he endeavored to present an encyclopedia of the knowledge of that epoch. It is especially reeking with pharmaceutical prescriptions for all kinds of disease.

During the first century of the Christian Era, there arose in Rome a small body of scientifically minded men, who strove to introduce a new development of medical theory. Their aim was to apply the Pneumatic Doctrine to physiology and pathology. The Pneumatist School, founded by Athenaios of Attaleia, contended that all phenomena depended on the vital air—the "*pneuma*." They studiously investigated the causation of disease and divided the etiological factors into extrinsic causes, intrinsic causes, and the causes due to evil spirits. Health, according to them, depends upon the normal condition of the *pneuma*, and is promoted by its tension, which is to be estimated by means of the pulse. Sickness is induced by a disturbance of the *pneuma* caused by

a faulty constitution of the elementary qualities, as, for instance, coldness or moisture.

We must not forget to speak a few words about that great and historically neglected physician of Greece, Aretæus of Cappadocia. Of him, Neuberger writes, "Whatever the final judgment may be, one thing stands out as certain—after Hippocrates, no single Greek author has equaled Aretæus, and no work in the entire literature so nearly approaches to the true spirit of Hippocratism, both in description of disease and in therapeutic principles, as the work of the Cappadocian."

Aretæus was a pure stylist in his language. He was not superstitious, and he endeavored to be rational and scientific. He described consumption and diabetes vividly. He treated of all the branches of medical knowledge. His contributions to the conceptions of nervous and mental disease are especially noteworthy. He knew that paralysis of central origin was crossed, while those of spinal origin are not. In the presence of a fatal malady, Aretæus writes, "When he can render no further aid, the physician alone can still mourn as a man with his incurable patient: this is the physician's sad lot."

The medical successor to Hippocrates and the scientific successor to Aristotle was Claudius Galen, the Prince of Physicians, who lived from 130 to 201 A. D. He was born at Pergamos, the son of Nikon, a well-to-do architect, who was a calm-mannered, learned man. "I was blest," wrote Galen, "with a calm, just, gallant and sympathetic father, whereas my mother was of so irritable a temper that she would at times bite her maids, and was forever screaming and quarreling with my father, worse than Xantippe with Socrates."

His father instructed Galen in mathematics and philosophy, and he learned under famous masters logic, dialectics, anatomy, empirics and medicine. He traveled to Corinth, Smyrna, Asia Minor, Alexandria, and after nine years of wandering he returned to Pergamos, where the reputation he had gained in foreign lands preceded him, so that he was received with open arms by his countrymen and was appointed by the High Priest, physician to the gladiators—a very honorable post for a young man of twenty-eight.

When he was thirty-two years old, the spirit of unrest again assailed him, and he sought to wander away from the cramped, provincial surroundings of his native town. An ambitious and brilliant man like Galen could be satisfied only in Rome, the capital of the world, and in the year 162 A. D., we find him a stranger in the Latin metropolis, struggling to establish himself. He succeeded very quickly, assisted as he was by some compatriots, and he soon became the fashionable physician, counting among his friends very influential men in the political, military and scientific circles.

Medical Rome was a city of specialists in those days, and from Martial we learn that certain men made a special practice of healing certain individual deformities or ailments. "Cascellius extracts and repairs bad teeth; you, Hyginus, cauterize ingrowing eyelashes; Fannius cures a relaxed uvula without cutting; Eros removes brand marks from

slaves; Hermes is a very Podalirius for ruptures." The medical profession consisted of charlatans, magicians, and nostrum venders, who extolled their wares to the public in the market place. Scientific medicine—even the so-called scientific medicine of that period—was unknown to the Romans.

Galen, who was far from being a modest and reserved man, attacked these professional quacks with a fury and bitterness characteristic of him. He called them fools and donkeys, and asserted that, "Whoever seeks fame by deeds, not alone by learned speech, need only become familiar at small cost of trouble, with all that I have achieved by active research throughout my entire life." These attacks so embittered his enemies that they plotted his assassination, and four years after his arrival he fled for his life from Rome.

Lucius Verus was then Emperor, and had not Galen left he might have then become Court Physician, for he had been introduced to court just before his flight from the capital. It is charged to the great physician that he left Rome not because he was afraid of his enemies, but because he feared the "plague" which was then beginning to scourge Italy. The royal family, whose ears had heard the praise of Galen, summoned him to Aquileia, where they were then sojourning. Marcus Aurelius, successor to Verus, appointed him his court doctor, and he retained this position under the reigns of the succeeding emperors, Commodus and Septimus Severus.

It would have made a more equable tempered man than Galen—who must have inherited a little of his mother's character—irritable to argue with the men who expounded the stupid "authoritative" knowledge of that time. Galen, who was eminently an experimenter and observer, who dissected apes, birds, fishes, reptiles and even an elephant, and who was an acute logician, must have fumed with impatience at the prevailing orthodox ignorance. Because a man lays his hand on his "heart" when he argues, it was asserted by Chrisippus that the heart was the seat of the soul, and that the voice emanates from the heart. It was fruitless for Galen to demonstrate that the contraction of the chest wall drives the air through the larynx, where the sound is modified by the contractions of this organ, due to nerve impulses. "When I tell them this," he complains, "and add that all voluntary movement is produced by muscles controlled by nerves coming from the brain, they call me *paradoxologos*, a teller of marvelous tales, and have no argument beyond the simple assertion that the trachea is near the heart."

In pathology and in nosology, Galen made distinct advances. Medicine he defined as the art which teaches the preservation of health and the cure of disease. With Hippocrates he believed in the doctrine of the humoral cause of disease, there being four humors—the blood, the phlegm, and the black and yellow bile. Disease consisted in "such a preternatural disposition or affection of the parts of the body, as primarily, and of itself, impedes their natural and proper action." The etiology of disease was divided into external and internal causes. The former were those due to the air, meat and drink, motion and rest, sleep

and wakefulness, retention and excretion, and the passions. These he named remote—procataretic—causes. The internal causes were to be arrived at by logical reasoning. The first of the internal causes was a vitiated state of the humors—a cacochymia—which may be characterized by a plethora of the humors, either a sanguinous, pituitous, melancholy or bilious, depending upon which humor predominates.

He classified symptoms as diagnostic and prognostic, describing certain signs as pathognomonic.

His work on the brain was purely experimental. He dissected the brain, and cut the spinal cord in living animals to observe the result. He did not believe the currently accepted theory that the only function of the brain was merely to cool the blood. The reason for this was his teleological proclivities. "In my view there is nothing in the body useless or inactive; but all parts are arranged to perform their offices together, and have been endowed by the gods with specific powers." And he, therefore, argued that the brain could not have the function assigned to it: "Why, if the brain is only a sponge, have we this complex structure, these membranes, blood-vessels, cavities, glands, nerves, when for the purpose of cooling only it ought to have been made like a sponge, inert and shapeless?"

Galen was the first to establish the fact that the kidneys secrete urine; he proved this by actually tying the ureters in animals, and observed that no urine was then secreted.

His works on diet, on treatment, on symptomatology and semeiology, on pathology, on anatomy, and on other related sciences are an everlasting monument to his memory. His influence on medicine was powerful until the seventeenth century, during which time to doubt Galen was to doubt an established religious tenet which was punishable by death. His errors—and he made many—were held to be sacred truths, and to quote Galen was to cite the most powerful authority. "Ipse dixit" of the Pythagoreans became the slogan of the followers of Galen. What he said none might venture to controvert.

Galen was the last and greatest of ancient physicians. In surgery, however, he did not excel.

In ancient days, when it was considered plebeian on the part of a physician to perform surgical operations, there of necessity developed a special guild of craftsmen whose business it was to treat undignified disease for which the learned doctors refused to prescribe. These empirics, the barber-surgeons and charlatans of yore, untrained in learned conversation, unacquainted with the writing of the philosophers, attained great skill in their practice. Empiricism is ever the beginning of true science. In the history of surgery there is no more interesting chapter than the story of these surgeons.

Rated on a level with the undertakers and embalmers, they pursued their unhonored profession, and, though lacking in dignity and lucre, they perfected their art and did much to alleviate human suffering.

In the famous oath which every physician swore to with reverence and fear, appears this clause: "I swear by the gods to cut no one for

the stone, but to leave this operation to those whose profession it is." This clause was inserted, not that the physician was unable to perform the operation, but that it was beneath his dignity to soil his fingers with immodest manipulations. Quacks and empirics were indeed grateful for this delicacy on the part of the doctors.

Though some surgery was practiced by most physicians, the operations of lithotomy and castration during the age of Hippocrates were relegated to the untutored empiric. The latter performed these operations while the physician and the priest stood by, the one recommending suitable ointments for the wound, while the other prayed to the gods to send a speedy cure.

Perhaps the greatest surgeon of antiquity was Antyllos, of whose life we almost know nothing. He must have lived in the second century of the present era. "He not only gave general directions for individual surgical operations, but discussed technical details with a minuteness and consideration of every conceivable eventuality only possible to a master of practice." He wrote on bloodletting, treatment of abscesses, phimosis, fistulæ, tumors, and he described in detail how to extract cataract and how to treat aneurysm by double ligature and incision.

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CHAPTER II

HISTORY OF MEDICINE DURING THE MIDDLE AGES

BY MAX KAHN, M.A., PH.D., M.D.

A pall of darkness settled over Europe with the fall of Rome. The civilized world was overrun by hordes of savage barbarians who destroyed cities, demolished edifices, and ravished and slew the populace. Luxurious Rome fell, and with it the unbearable tyranny of the Cæsars.

“Rome shall perish! Write that word
In the blood that she has spilt;
Perish hopeless and abhorred,
Deep in ruin as in guilt.”

From the East and the North, the Huns and the Goths and the Norsemen invaded the territory and conquered the decaying civilizations of the South. The beauty and elegance of the towns were superseded by the brutality and coarseness of the camp. From the fury of the savage none escaped. Libraries and temples, seats of learning and places of worship had no intrinsic value to the nomadic races, who swarmed over Italy, and demolished everything which they could not carry away.

The conquering savages were converted ultimately to Christianity. In Spain, for instance, the tribes of the Suevi and Visigoths were the victors, and they formed the rallying ground of the Aryan heresy of the Christian Church for one hundred and fifty years. North of them, the Franks who had been converted to the orthodox creed, encouraged by the Roman clergy, waged war against them. The Church became all powerful. As Buckle¹ writes: “Late in the sixth century, the Latin clergy converted their Visigothic masters, and the Spanish government becoming orthodox, naturally conferred upon its teachers an authority equal to that wielded by the Aryan hierarchy. Indeed, the rulers of Spain, grateful to those who had shown them the errors of their ways, were willing rather to increase the power of the Church than to diminish it. The clergy took advantage of this disposition. . . . The ecclesiastical Synods became not only the councils of the Church, but also parliaments of the realm.”

Everything pagan was forgotten. The clergy discouraged the possession or the study of books written by the ancient Greeks or Romans. They held in abomination their sculpture and their works of art, their rhetorical lectures and their philosophical speculations. For the early Christian was an ascetic. He passed through this vale of tears only to be weighed in the scale, and adjudicated worthy or unworthy of

paradise. He feared much to be found wanting. Worldly joys, earthly beauty, sensuous pleasures, pagan learning, metaphysical discussions, were all abhorred as a temptation of the devil. It was dangerous to know too much. "Vanity of vanities, all is vanity." All wisdom was in the Bible, and all endeavors were directed to purging the soul of sin. The rich, the pleasure-inclined, the animal-spirited, had no chance of entering the Kingdom of Heaven. It was only the fallen, the suffering, the poor, to whom it was vouchsafed to enjoy everlasting happiness after death. In the Emperor Julian, the Apostate, we notice the revolt of the individual post-Hellene against the lack of beauty of the Nazarene faith. In his drama, "Emperor and Galilean," Henrik Ibsen depicts the struggle that went on between the beauty-loving Greek and the ascetic, aggressive Christian. What has been said of the attitude of the Moslem rulers toward learning, may have been written with greater justice of the intolerance of the Christian clergy of that period. It has been represented that the Caliph Omar, upon being requested by his general, Amrou, to spare the library of Alexandria, issued the following order: "If these writings of the Greeks agree with the Koran, they are useless and need not be preserved; if they disagree, they are pernicious and ought to be destroyed." It is doubtful whether the Caliph ever made such a ruling, but it would tally with the spirit of the times if we had read that some Bishop had issued a similar command.

The Greek and Latin written contributions to civilization were saved by the advent of the victorious Mohammedan armies into Europe, which carried in its wake the various educational and scientific influences that were to affect the whole course of later European culture. The Saracens brought to Spain, under the protection of the banner of the Crescent, the stored-up treasures of ancient learning. While church-ridden Europe reposed, ignorant of the wealth of knowledge and wisdom that the pagan writers had left as an inheritance to civilization, the peaceful Arabs and Moors interpolated their studies of the Koran with readings from the Arabic translations of the Greek and Roman philosophers. Unlike the earlier Moslem warriors, the Saracens preserved and cherished the treasured volumes which they found in the conquered cities. The most approved writers of the Mohammedans admit and even declare in the most explicit terms, that "the religious books of the Jews and the Christians which are acquired by right of war should never be committed to the flames, and the books of profane science, historians or poets, physicians or philosophers, may be lawfully applied to the use of the faithful."²

This tolerance of the Arabs was the saving grace of civilization. They relit the lamp of learning which had been extinguished in Europe, and the light of Hippocrates, Aristotle and Galen illumined the mosques and cloisters of the infidels. There science flourished, and there the art of medicine was given a new lease of progress. In the year 711, after the battle of Xeres de la Frontera, the victorious Saracens captured the Pyrenean peninsula, and brought back to western Europe the ancient learning.

The Byzantine period was particularly sterile in its contributions to knowledge. In medicine and in philosophy strict adherence to the teachings of the orthodox school was enforced. "As in life, so in letters, outward form and attractive appearance weighed most heavily in the scales and the disparity between bombastic rhetoric and dialectic juggling on the one hand, and the intrinsic barrenness of these on the other, imparted to the literature of the Byzantines those characteristics of formality, artificiality and pharisaic insincerity which have become proverbial." There was no independent thought, no search for new paths, no original investigations. Again, in the absence of learning, superstition held supreme sway, alchemy flourished, and astrology and mysticism were in vogue.

During this period we find three medical authors who are representative of the mediocrity and stereotyped "wisdom" of that era. *Ætius*, who was born during the sixth century at Amida in Mesopotamia, was physician to the Imperial Court of Byzantium. He has left to posterity a compilation known as the "*Tetrabiblon*," which is a compendium of his medical and surgical knowledge. His works abound in external remedies; and nearly an entire book is devoted to the preparation of plasters. He introduced the doctrine of spells, relics and incantations into medical therapeutics. For the removal of anything sticking in the throat, he advised using the finger of St. Blazius. At that time there developed a traffic, which must have been very active, in pieces of the true cross and in tears that the Virgin Mary had shed. These were supposed to have remarkable curative powers. As somebody has well said, "A grove of an hundred oaks would not have furnished all the wood sold in little morsels as remnants of the true cross; and the tears of Mary, if collected together, would have filled a very large cistern." Even at that time, the sellers and makers of this merchandise must have been very cynical individuals. "The idol carver worships not; he knows what gods are made of."

Ætius treated gout by the following regimen, which is given as an example of the absurdity of practice of the middle ages: In September, the diet should be wholly milk; in October, garlic must be eaten; in November, bathing is prohibited; in December, cabbage is interdicted; in January, the patient should take a glass of pure wine every morning; in February, he must not eat beet; in March, he must mix sweets with his food and drink; in April, he must refrain from horse-radish; in May, he must avoid the fish called *Polypus*; in June, he must take cold water in the morning; in July, he must abstain from venery; and in August, he must refrain from eating mallows.

A greater man than *Ætius* was Alexander of Tralles, who was either a Jew or a Christian, but not a pagan. He was born in 525 A. D. His writings are in pure Greek, and rival the literary clarity of *Aretæus*. In his expression of opinion and originality of observation, he reminds us of the men of the Age of Pericles, and one delights to meet such a refreshing current in the stagnant pool of Byzantine culture. Defending certain radical changes in therapy that he recommended in

contradiction to Galen, he writes: "Here may be applied the saying of Galen concerning Archigenes: 'He was a man, and it is, therefore, difficult to assume that he never made mistakes, since he must have been ignorant of many things, have misinterpreted others, and described them superficially.' Yet would I not have dared to say this of a man who stood so high in science, if truth had not inspired me with confidence, and if I had not held silence to be a sin. For, if a physician form an opinion and fail to express it, he does a great wrong, behaves wantonly, and by his silence is much to blame. Herein one should follow the principle which, as he tells us, Aristotle has laid down: 'I love Plato, but I also love truth, and so if choice must be made between them, I give preference to truth.'"

Still, he was a child of the times, for he believed in magical practices, if all else failed. He advised spiritual incantations, laying on of hands, calling up of the dead, and other mystical measures, which we can only deplore in so great an original thinker. He wrote only of what he had seen and experienced. He avoided writing about diseases and therapeutic remedies he had never tried out or observed himself, so that all his writings are an epitome of his own personal experience. He attempted to differentiate between pleurisy and inflammation of the liver, between intestinal and renal colic, between hectic and other fevers. For the treatment of gout he recommended *Colchicum autumnale*. He wrote on the eyes, on fractures, on various mental diseases, on fevers, etc. He described the lumbrici, the ascarides and the tænia parasites of the intestinal tract.

Contemporary with him, there lived Jacobus Polychrestus and Isidore of Gaza. Polychrestus was ennobled by the Emperor Leo the Great for his great learning, and a statue was erected in his honor by order of the Senate. He was famed for his skill and for his preference for the employment of enemata and suppositories rather than for the use of the knife. So cherished was he, that he was called "The Beloved of God."

Paulus of Ægina, who lived in the seventh century, wrote voluminously on medicine. He was the first to advance the theory that gout is a disease of nutrition. According to his view, "as a result of insufficient assimilative powers of various parts of the body, there is formed from the superfluous food, together with indolent habits of life, a morbid humor, which is first attracted by a weakened joint, but may also lodge itself in the liver, kidneys, spleen, etc."

With the decay of Byzantine civilization, there was a general cessation in the progress of all science. The superficial gloss that replaced true culture evinced itself in the shallow writings of that time. The increased power of the church augmented its intolerance of all that was an innovation, with the result that human endeavor was held in abeyance. There was a dearth of originality, and the ingenuity and talent of those that were exceptionally proficient were wasted on purposeless tasks.

Theophilus, with the characteristic empty verbosity of the school-

men who exercised their reasoning faculties on determining how many angels can dance on the point of a needle or which way the mule will turn on being placed between two bales of hay, wrote a treatise on the examination of the pulse and on uroscopy. Another author, Jeannes Actuarius, who lived in the thirteenth and fourteenth centuries, also wrote voluminously on the examination of the urine and on sphygmology. In his monograph "On the Urine," many kinds of sediments are named according to their colors and consistencies, and graduated glasses for the measurement of these deposits are described.

We shall eschew enumerating other Christian physicians who practiced more magic than medicine, and who were more superstitious than scientific. The Arabs, having drunk of the fount of Hellenic and Latin culture, produced great men who not only kept intact the ancient inheritance, but also added much to it, and handed it on worthily to their successors. The Moslems, however, were held in utter religious and political hatred by the Western Europeans, and it was only the Jews who brought to the principal Frankish towns the Asiatic knowledge. Many courts had their Jewish physician, and while they may have persecuted his brethren, the rulers kept the Hebrew doctor safe from all harm, and occasionally showered honors upon him.

Arabian Medicine has its Hippocrates in the great Rhazes, who was born in 852 at Rei, a city of Persia. He studied at Bagdad, and then traveled through many countries, studying and observing, and, like Bacon, made all Nature his study. He attained to great dignity, becoming Court Physician and the friend of princes. He died in 932, poor, blind and friendless. Arabian writers praise him exceedingly. Abi Osaiba stated that Rhazes had written no less than two hundred and twenty-six books. There is no doubt that he was a man of rare parts, a versatile writer and an inspired teacher. His great work, "Al-Hawi," or the "Content of Medicine," is an evidence of his tireless industry. In his teachings and practice he followed Hippocrates and Galen, but he has given to posterity not only vague speculations, but also exact and practical observations. Like many men of the Orient, he cautioned against drastic measures in the treatment of disease. "At the commencement of an illness," he wrote, "choose measures whereby the strength may not be lessened." "Where thou canst cure by diet, use no drugs, and where simple measures suffice, use no complex ones." The state of the psychology of the populace regarding medicine and physicians is very shrewdly portrayed in the following extract made by Neuberger from Rhazes' treatise, "Upon the circumstances which turn the hearts of most men from reputable physicians":

"Among those factors which make the people turn away from the intelligent physician and place their trust in impostors is the delusion that the physician knows everything and requires to ask no questions. If he inspects the urine or feels the pulse, he is supposed to know what the patient has eaten and what he has been doing. This is lying and deception and is only brought about by trickery, by artful questions

and speech, through which the senses of the public are deceived. Many hire men and women to find out all the circumstances of the patient and to report what is told them by the servants, friends, and neighbors. I, myself, when I began to practice medicine, had resolved to ask no questions when the urine had been given me, and had been much honored. Later, when it was seen that I made circumstantial inquiries, my reputation sank.

"Another circumstance which brings the physician into contempt is that many diseases are too little removed from the border line of health and are thus difficult to recognize and to cure; others, malignant in themselves, externally appear trivial. When the layman sees that the physician is in doubt concerning his cure, he draws it as certain inference that the physician will understand still less of severer and more extensive illnesses. . . .

"But the well-trained physician is also very often in doubt, and may take a very long time to find the proper remedy. . . . A physician is sometimes undervalued who takes trouble over an incurable complaint; but the imperfection of the art should be considered, in this respect unlike other arts, of which men know more than is necessary, while in medicine men have not yet attained to the indispensable and do not possess a remedy for every ill. The fault is, therefore, with the art, and not with the physician. The public demands that the physician should cure in a moment, like a magician, or that he should at least employ pleasant remedies, which is not all times and in all cases possible; to blame the physician on Nature's account is a great injustice."

Rhazes described the symptoms and course of hydrophobia. He was the first to treat expressly of the diseases of childhood. He wrote learnedly on erysipelas, small-pox and measles.

But if Rhazes was the Father of Arabian Medicine, his successor, Avicenna, was the greatest light of that school, and far exceeded his medical progenitor. He was born at Bokhara in the year 980. From childhood on he applied himself to the study of mathematics and natural philosophy. His knowledge of medicine was profound, so that he soon became famous not only in the city of Ispahan, where he lived, but in all Mussulman countries. He was a man who was given, however, to worldly pleasures, so much so that he was much censured during his life, and the Arabs have since the proverb, that neither the study of philosophy contributes to virtue, nor that of medicine to the preservation of health. When only 56 years old, he died (1036), and was buried in the city of Hamadan, where his grave is pointed out to this day.

The *magnum opus* of Avicenna is the "Canon," the reputation of which at once superseded the "Al-Hawi" of Rhazes and the "Kingly Book" of Ali Abbas, and even the writings of Galen. This is the first codification of Græco-Arabic medicine, presented in a lucid, sparkling style, classified and analyzed so that it becomes easily accessible to the reader. He attempted to make a mathematical science out of medicine, and he especially ridiculed astrology.

In the writings of the great Jewish physician, Maimonides, whose work was based on Avicenna's "Canon," and whose books, in translation, were used in European Universities for several centuries, we can find all that Arabian physicians have contributed to Medicine, as well as an epitome of the Talmudic medical lore.* It is instructive to study the life of this great teacher and doctor.

Of all the cities of Spain which submitted to the Moslem yoke, Cordova especially excelled in commerce and in letters. There, in the houses of learning, men of fame studied and taught, and there, also, in 960, the Jews founded their first Academy. The Moors and Hebrews lived in peace with one another, and good-naturedly endeavored to outrival each other in literary and philosophical attainments. In the twelfth century, Cordova was at the zenith of its glory under the prosperous reign of the noble Abderhaman.³ Maimonides, who was born in Cordova in the year 1135, was the son of generations of judges and rabbis. The Jews had already produced a number of great men in Moorish Spain. There was Jehuda Halevi, born in old Castille in 1085, who is the Hebrew prince of poets. He was a busy practitioner, and though he is famous for his poetry and philosophy, his livelihood was obtained by practicing the medical art. There were also Ibn Alamani, Samuel ben Chanania, Ibn Timmon, Ibn Algami and others—men who had created for themselves an enviable following among Jews and Moors alike.

It was not destined, it seems, that the calm peace and contentment should continue without interruption in the Saracen towns of Spain. From the northern coast of Africa there came a fanatic band of destroyers, who proceeded with fire and sword to reclaim peaceful Spain and turn it into a very den of chaos, where intolerance was boasted of, and where lack of conformity to the Islam faith was punished by death unless the "unbeliever" had the good fortune to exile himself ere the hand of the Mosque was laid upon him. Under the leadership of Yussof, son of Teshfin, who was influenced by certain zealots, the Almoravids, a fierce and war-like tribe waged warfare against the peaceful inhabitants of Spain. They were entirely successful in their ventures, and in 1148 they conquered the beautiful town of Cordova, and vandal-like, destroyed its beautiful buildings and drove out all who would not accept Islamism.

The family of Maimonides became a wanderer on the face of the earth. In 1159, we find them in Fez, where, though they persisted in the Hebrew faith, they were left unmolested. When twenty-three years of age, Maimonides began a Commentary on the "Mischna," which, after a laborious study, he completed in 1168. In his writings and explanations, he was often at variance with his predecessors and contemporaries, who delighted to indulge in luxuriant phraseology and

* The Talmud is the collection of Jewish legal knowledge, written during the second to the sixth centuries after Christ. The medicine in the Talmud, while it is copious, is unsystematic, since it was not intended as a treatise on medicine, but on the relation of health and disease to the Hebrew ritual and to civil and criminal law. The greater portion of the medical sayings are ascribed to Mar Samuel of Babylonia, who lived from 160 to 257 A. D.

vague symbolic blandishments. He made it his aim to eschew prolixity for brevity, and to confess ignorance where positive knowledge was not forthcoming. It was he who said that it was possible for a wise man to be taught by a fool, and he was fond of remarking to his scholars: "Teach thy tongue to say, I do not know."

He also was typical of the time in which he lived. He wrote on astrology, on metaphysics, on general philosophy, on religion and the law, and on medicine. While in Fez the Maimonides family thrived well in wealth. David, his brother, was a diamond merchant and was quite successful in his undertakings. While in Cairo, where Maimonides later resided, his father died. His brother perished at sea during one of his voyages to the Orient, and with him the whole wealth of the family was lost, which circumstance left Maimonides without financial support, and he was compelled to earn his own livelihood. He adopted the medical profession, and after several years of practice, became the recognized authority on matters medical. He was appointed private physician to Saladin's Vizier, and later Court Physician to the Sultan himself.

Maimonides was a very busy and conscientious practitioner. We can obtain a glimpse into the busy life of the famous doctor in perusing a letter that he wrote to his friend, Samuel ibn Tibbon: "I live in Egypt at a distance of nearly two Sabbath day journeys from Cairo, where the Sultan resides. The duties of my appointment demand regular attendance upon him every morning. If there is nothing amiss at the court, I return home toward noon, almost famished for want of food; on my return, I find the approaches to my house crowded with Gentiles and Jews, men of all ranks, impatiently awaiting my return. As soon as I have taken refreshment, I examine my patients until I am become so overpowered with the fatigue of speaking and prescribing that my speech almost fails me before I can conclude." In a letter to a favorite pupil, he writes: "You know how difficult this profession is for one who is conscientious and exact and who states only that which he can support by argument or authority."

The purpose of medicine, he considered, "was to teach humanity the causes of ill health, the correct dietetic hygiene, the methods of making the body capable of useful labor, how to prolong life, and how to avoid disease. It thus directly elevates the human being to a higher moral plane where the pursuit of Truth is possible and where the happiness of the Soul is attainable."

In his great "Book of Law," he devotes a chapter to the medical art. He recommends certain dietetic rules, following the prevalent medical theories of his day. It is interesting to examine, even if cursorily, these regulations in dietetic hygiene:

"Sound health of body is an unavoidable prerequisite in the development of the soul. It is, therefore, the duty of all persons to avoid all harmful things. One should eat and drink only when one has hunger or thirst; but even in these cases one must not fill his belly full, but allow about one-quarter of the appetite to remain unsated. Dur-

ing meals one should not drink water; one might use a little wine mixed with water. The wines are harmful in youth, but may be tolerated in age. In summer one should partake of cold food and little of vegetables; in winter, the opposite. Certain foodstuffs are especially harmful, and it is wise to neglect them, for example, large fish, cheese, and meat which are old and are preserved in salt. Sour fruit is not to be eaten; unripe fruit acts upon the body like a sharp knife. . . . Bathing should be indulged in once every seven days. A person should sleep eight hours. During the day one should not sleep. Disease will not attack him who lives moderately. Among a thousand persons, only one dies a natural death; the rest succumb early in life to ignorant or irregular behavior."

Maimonides closed his dissertation with the following words: "I assure the person who will follow my precepts that he will not suffer bodily pain and that he will not require the services of a physician. He will retain his powers and his faculties all through a long life, and at extreme age, he will die a natural death. These regulations are always valid. They, however, who since birth have suffered from a bodily ailment or who in youth have accustomed themselves to evil practices, will do well to read the 'Book of Remedies,' which I am now preparing."

Hygiene was the favorite theme for discourse, especially food hygiene. He was one of those who believed in the avoidance of disease rather than in the cure of it. In his "Guide to the Perplexed," he states that the variety of food taken by an individual should not depend upon his taste and caprice, but upon certain dietetic principles, whose aim it is to enhance the health and usefulness of the body. One should not accustom one's self to the foods which tickle the palate, but should always keep in mind the desirability of prolonging life and increasing health. One should, therefore, eat of wholesome food, whether sweet or bitter. Exercise, he asserted, has in certain cases a decided beneficial effect. They who follow only sinful inclinations lower themselves to the form of brutes. "For those gifts of intelligence and judgment with which he—the human being—has been endowed for the purpose of acquiring perfection, but which he has failed to apply to their proper aim, are used by him toward wicked and mischievous ends; he begets evil things as though he merely resembles man or simulated his outward appearance."

Among the extremely orthodox, there was a certain group at that time who thought it sinful to consult a physician. Disease, they argued, was a manifestation of the anger of the Lord, and in order to become cured it was necessary to fast and pray and make amends, but not to use medicinal herbs, or other therapeutic remedies. The use of these, in their opinion, smacked too much of insubordination to the divine power. Maimonides, on the contrary, strongly urged upon the community the benefits to be derived from medicine: "A person should not reside in a neighborhood where a physician does not dwell," was one of his recommendations. Among the absolute requirements of a

municipality were the physician, the surgeon and the bathhouse. He was especially particular to point out the apocryphal law that the physician shall be used in times of illness.* "Like unto a murderer," he wrote, "is the physician who refuses to tender his assistance in times of necessity, or who practices without due study of the ailment which he is treating."

Unlike the Christian physicians, Maimonides opposed secret, magical or mysterious remedies: "You must beware," he wrote, "of sharing the errors of those who write amulets. Whatever you hear of them or read in their works, especially in reference to the magic names of God, which they form by combination,** is utterly senseless; they call these constructions holy names, and believe that their pronunciation demands sanctification and purification, and that by using them they are enabled to work miracles. Rational persons ought not to listen to such men nor in any way believe their assertions." In another chapter he pleads strongly for progressive scientific and philosophical investigations: "It was not the object of our prophets and our sages to close the gates of investigation entirely by these utterances,† and to prevent the mind from comprehending what is within its reach as is imagined by simple and idle people, whom it suits better to put forth their ignorance and incapacity as wisdom and perfection, and to regard the wisdom and distinction of others as irreligion and imperfection, thus taking darkness for light, and light for darkness."

It has been said that Rambam‡ was the most rational physician of the Middle Ages. As Muenz states, his desire was to give clear reason precedence over vague mysticism. "The eyes," wrote Maimonides, "look forward, not backward." Like Rhazes and Avicenna, he was an enemy of complicated, odious medications. "In minor ailments," he wrote, "Nature cures the body without the need of medicinal remedies, if the patient follows only certain dietetic regulations. Where, however, the services of a physician are required, he should see to it that he aids Nature in her beneficial course. Most of the doctors err in their treatment. In endeavoring to assist Nature, they weaken the body with their prescriptions."

Perhaps the most important medical work of Maimonides was his abbreviated edition and translation of Galen. He systematized the writings of the Pergamite, and commented on those chapters which he thought worthy of special note. Like his Arabian predecessors, he did not blindly follow the teachings of Galen, but on various occasions took issue with him.

* Ecclesiasticus, xxxviii, 1 to 15.

** Abracadabra, and other similar words.

† "Neither make thyself otherwise; why shouldst thou destroy thyself?"—*Ecclesiastes*, vii, 16.

"It is not good to eat much honey (learning)."—*Proverbs*, xxv, 27.

"Do not inquire into things which are difficult for thee; do not search what is hidden from thee; study what thou art allowed to study, and do not occupy thyself with mysteries."—*Book of Ben Sira*, iii, 18.

‡ Rambam is the name given to Maimonides. It is the collection of the initial letters of his name, Rabbi Moscs Ben Maimon.

The "Sefer Refuoth," or "Book of Remedies," must needs be reckoned his most widely known, though not most important contribution to medicine. In this book he relates the case of a woman who suffered from stomach disease. All the remedies that had been suggested to her she had tried, but they had proved of no avail. "I prescribed," he wrote without intent to boast, "for the patient that which, no sooner had she taken it, than she became stronger and her appetite returned." In another place he relates the medical history of a young man who suffered from a disease of the brain membranes; "with the help of God," he was able to cure him.

The appointment of Maimonides to the position of chief physician to the Sultan carried with it the envy and enmity of the other court doctors, astrologers, and magicians, of whom Saladin seemed to have had a goodly store. But Maimonides was always courageous. His good faith, his knowledge and his wisdom stood him in good stead, and he was able to withstand the machinations of his enemies. When his daughter and his beloved pupil died, he almost lost hope, and grieved so profoundly that he became desperately ill. In a letter, which he wrote to his son Abraham, who was then in Spain, we see the anguish and despair of the great sage: "My son, the great labors of studying and writing and the immense responsibilities of my position in court, as well as the cares of the family, have worn me out so that I am now on the bed of disease. My enemies are alive and mighty, the number of my haters is great, and the death of your sister and my beloved pupil has increased my sorrow a hundredfold."

In 1193, Saladin the Great died, and the sun of the fortunes of Maimonides became somewhat obscured. However, with the ascent of the Sultan Almalik Alafdel to the throne (1198), the horizon cleared, and Rambam was again clothed in the great dignities and honors that were his before.

This sultan was a sickly prince, whom dissipation and debauchery had weakened both in mind and body. Maimonides had indeed here a royal patient suffering from many real and imaginary, corporal and mental ailments. Nevertheless, the physician did not permit that the royal station of his patient should in any way interfere with his method of treatment. He was strict, and he endeavored to cure the soul of the prince as well as his body. He concluded one of the letters that he wrote to this monarch in these words: "May God in his mercy increase the number of the days of my lord, and strengthen his health, and grant him happiness of soul *here* and *there* according to the sincere prayers of his servant, Moses ben Maimon."

The sultan suffered with asthma, and Maimonides made a special study of this disease, which he later published in a "Treatise on Asthma." At about this time the Mesir Alfadhel requested Maimonides to write a discourse on poisons and their treatment. The cause for this request was the prevalence of disease in Egypt induced by the bites of animals, especially snakes. Maimonides in his introduction to this essay pretended to no originality, but stated that he had compiled all that

was known in his time about the treatment of poisoning and that he had endeavored to present this to his reader in a concise and succinct form. The book consists of two divisions. The first is divided into four sections and deals with the treatment of the bites of animals. The second division, consisting of six chapters, treats of the manner of antidotal administration for internal poisons.

Some of his recommendations are the following: The wound induced by the bite of a poisonous animal should be sucked dry by the lips, should be kept open, and alcohol and oil should be applied. Emetics should be promptly administered. He suggested various applications to the wound, among which were common salt, onions, asafetida, etc. For internal poisoning he advised the use of mandrake, bezoar, precious stones, various aromatic principles, and especially theriaca, which in all times was believed to possess properties of combating the effects of the bites of venomous animals.

He wrote on hydrophobia, on sexual diseases, on hemorrhoids, on gout, on the causes of disease, etc. His fame was so great that foreign monarchs requested his advice and followed his prescriptions. It is said that Richard Cœur de Lion desired to take him to England as his Court Physician, but the Hebrew doctor declined this honor. The fame of Rabbi Moses ben Maimon was very great during his lifetime, and after death all nations united in lauding him. He has been called the "Eagle of Doctors," "*Lumen Captivitatis*," and "*Moses Ægyptius*." All his successors had naught but praise for him after his death. The Arabic poet and Cadi, Al Said ibn Surat al Mulk, sang his praise in ecstatic verse:

"Galen's art heals only the body,
But Ibn Amram's the body and the soul.
With his wisdom he could heal the sickness of ignorance.
If the moon would submit to his art,
He would deliver her of her spots at the time of full moon.
Cure her of her periodic defects,
And at the time of her conjunction save her from waning."

Maimonides died in the sixty-ninth year of his life (1204) in Fostat, where both Jews and Mohammedans observed public mourning for three days. His body was taken to Tiberias for interment and his tomb became a place for pilgrimage.

Abulkassim, Avenzoar and Averroes were also Cordovans. Abulkassim's writings give us an insight into the surgical technic of those days. Avenzoar was born toward the end of the eleventh century. He was a decided foe of quackery, and his advice to his scholars was that "experience is the best guide and test of practice; and that every physician conforming to this test would be acquitted both here and hereafter." He experimented on goats and other brutes. He stated that he had practiced bronchotomy on goats and that it was a feasible operation. For obstruction of the esophagus, he advised either the passage of a tin or silver tube through which the patient can be fed, or feeding the patient by means of inunction or bathing in milk or other nutrient

fluids, or by administering nutrient enemata. The last method he used in a pregnant woman for six weeks' time with complete success. Avenzoar died full of years in 1162.

Averroes (Ibn Roshd) was born in Cordova in 1126. He was the son of the High Priest and Chief Justice of Cordova, and was educated in the University of Morocco. His religious skepticism and his love for the pagan learning led to his persecution and exile. Even the Christians were against him in the succeeding centuries. He was spoken of as "the mad dog who barked against the Christ," and was called by Erasmus "impious and thrice accursed." He died in 1198 in Morocco. Mediæval writers have given him the title of "The Commentator," *par excellence*, for his writings aim to restore the philosophy of Aristotle and Plato.

These men broke somewhat the pall of theological darkness that covered Europe, and men were born in England and Italy, in Spain and in France who revived learning, and sought to study Nature by experimentation and investigation. This awakening marks the beginning of the modern period, when men followed the advice, "Ye shall know the Truth, and the Truth will make ye free." With Roger Bacon, the Englishman, who was intellectually three centuries in advance of his time, we find the culmination in Europe of Arabian knowledge. He, however, was not a medical man, but the path that he had hewed during a life of persecution and suffering was much widened by the scholars that followed him.

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CHAPTER III

HISTORY OF MEDICINE DURING THE SIXTEENTH AND SEVENTEENTH CENTURIES

By MAX KAHN, M.A., PH.D., M.D.

The era that produced Columbus and Savonarola and Leonardo da Vinci is the most illustrious in Italian history. The reawakening of Europe from its lethargy of so very many centuries is especially evidenced in the strivings and teachings and writings of these men. The Genoese navigator felt the spur of the times, irked at the circumscribed limitations of the physical world, and ventured forth on the great unknown Ocean to peer into the mystery of the Beyond, and to uncover the vast continents that had been hidden hitherto to civilization.

The Doctor Faustus of the fifteenth century is Leonardo. In the portrait that we have of him, we see a venerable man, with a long flowing beard, a high forehead, and a face full of wisdom and learning. It is the face of old Faustus, who having studied much and learned much, sees the narrow confines of his world, and seeks higher altitudes and wider horizons for his contemplation:

"I have, alas! Philosophy,
Medicine, Jurisprudence, too,
And to my cost Theology,
With ardent labor, studied through.
And here I stand, with all my lore,
Poor fool, no wiser than before.
Already these ten years I lead,
..... and learn
That we in truth can nothing know!

Woe's me! still prisoned in the gloom
Of this abhorred and musty room!
Where heaven's dear light itself doth pass
But dimly through the painted glass!"

Pious, ascetic Girolamo Savonarola might, indeed, preach against the profligacy and immorality of the period in which he lived. With Hamlet, he might have exclaimed,

"O cursèd spite,
That ever I was born to set it right."

For the times were unsettled and ungodly, and the world was reeking with rottenness and corruption. The fourteenth and fifteenth centuries

have been called the Age of Despots in Italy. Tyrants, deriving their power either by heredity, or by pretended authority on the basis of imperial right in Lombardy, or through their power as chief of some military force, or through their wealth, established dynasties in the various principalities and cities, oppressed the burghers with heavy taxes and cruel laws, until some more formidable tyrant of some neighboring town waged war against them, and substituted his despotic rule in their stead. In such times of strife and turmoil which were characteristic not only of Italy, but also of all Europe in that period, it is not customary for Arts and Science to flourish, and the reason for the literary and scientific prosperity in Italian cities is to be found in the personality of the very tyrants that caused all the misery of the masses.

In Italy, the personality of the individual—his mentality, his ruthlessness, his physical prowess, his command of men—was considered of more account than his family tree, or his legal privileges or his moral rights. Illegitimacy of birth was not deemed a blot on the escutcheon of a powerful leader. "The last La Scalas were bastards. The House of Aragon in Naples descended from a bastard. Gabriello Visconti shared with his half brothers the heritage of Gian Galeazzo. The line of the Medici was continued by princes of more than doubtful origin. Suspicion rested on the birth of Frederick of Urbino. The houses of Este and Malatesta honored their bastards in the same degree as their lawful progeny."

The tyrants of Italy were usually able men, if they were quite frequently merciless and treacherous. They vied with one another in the brilliancy of their courts. To drive away the malign fears and evil fancies which frequently tortured their conscience, they surrounded themselves with men of letters, artists, musicians, astrologers, and buffoons. Certain of them—Gian Galeazzo Visconti, Can Grande della Scala, Francesca and Ludovico Sforza, and others—fostered the foundation of libraries, the building of palaces, the adornment of churches, and patronized all the sciences and arts. "The life of a despot was usually one of terror. He surrounded his person with foreign troops, protected his bedchamber with a picked guard, and watched his meat and drink lest they should be poisoned. He dared not hope for a quiet end. No one believed in the natural death of a prince; princes must be poisoned or poniarded." Since he had no friends, the tyrant invited entertainers—artists or alchemists, philosophers or buffoons—whom he could patronize, and whose devotion and gratitude he could buy.

Toward the latter part of the fifteenth century, the court of Florence under the rule of Lorenzo di Medici was the most brilliant. Francesco Guicciardini, one of the friends of Pópe Clement VII, has said that "if Florence was to have a tyrant, she could never have found a better or a more pleasant one." Lorenzo had no compunction in elevating the very lowest to the very highest office, if he thought the person merited promotion. In this court, Leonardo da Vinci (the bastard son of a

small noble) at the age of eighteen became one of the artists, and he resided there for twelve years, until 1482.

Successively under the patronage of the Dukes of Milan, Mantua, and Florence, the King of France and the Pope, Leonardo traveled from city to city, until finally he settled in Paris. The King of France, in hopes that the great Italian had many more years to live, gave him a salary of seven hundred crowns a year, and appointed him architect, painter, engineer and mechanic. But Leonardo's life was fast ebbing. His right hand became lame. In a drawing that he made of himself at about this time, we see an aged man seated amid a landscape, absorbed in melancholy reflections. A little later we see him as he depicts himself in the well-known portrait at Turin. "An unkempt, time-worn and weather-beaten man, with long wisps of scanty gray hair falling about his head and face, and a nose which overhangs the upper lip of a toothless mouth, whose corners droop as though distorted by pain." It is Faust that we have here before us, Faust to whom all his labors of research have brought but the one certainty—that the knowledge he seeks is unattainable. Isolated and apart, the whole earth was powerless to offer him that which he sought. "Where the depth of feeling is the greatest, the martyrdom also is greatest," he once wrote in his diary.

A patron of art who visited him in 1516 describes the studio in which Leonardo lived, like an ancient magician, amid a confusion of retorts, flying machines, skeletons, stands and chemical apparatus.

On May 2, 1519, Leonardo passed away. Sixty poor people who had experienced his charity followed the funeral procession with torches. Francesco Melzi, his literary heir, announced his death to his family at Florence, with the words: "Every one mourns with me the loss of a man such as Nature is powerless to create a second time."

Born at a time when the world was just entering upon the Modern Era, Leonardo was mentally very much in advance of his epoch. He studied, experimented and then drew conclusions. No accepted dogma, no conventional belief, no current supposition was taken for granted. With almost superhuman power he delved into all the scientific mysteries and seldom failed to bring forth lucid explanations of what seemed to others of his time inexplicable phenomena. Alexander von Humboldt has said of him, "He was the first to start on the road towards the point where all the impressions of our senses converge in the idea of the Unity of Nature."

Leonardo was a Greek of the Age of Pericles, who lived in the time of Savonarola. It is said of him that he had given up his Christian faith when he was at Cairo as Engineer to the Sultan.

Merezhkowsky has well portrayed Leonardo da Vinci. He represents him as mocking both the alchemist and necromancer as well as the ascetic and religious. He pictures (with poetic license) Leonardo listening to Savonarola haranguing the masses to turn away from worldly pleasures, and while the crowd fears and trembles and shrieks "*Misericordia, Domine, misericordia,*" he (a faint smile lurking about his lips)

draws a caricature of Savonarola. "He purged Christian art of its pessimism, its depression of spirit, and its asceticism. Youth is stamped on all his work. It is true that Leonardo also painted the mysteries of the Catholic faith, yet, before his 'Last Supper,' we are reminded of Plato's feast and the School of Athens—of Greek philosophers, not of the inauguration of Christian Sacrament. And not only that, but beneath the figure of Christ, mild, gentle, self-sacrificing, he inscribed the legend, 'Ecce Homo!'; while below the equestrian statue of Francesco Sforza, the erstwhile peasant-lad, who—thanks to his good right arm—sat before his death on the ducal throne of Milan, he engraved the proud inscription, 'Ecce Deus!'"

It is claimed by Séailles that Da Vinci introduced the experimental in science, and while Bacon may have more influenced posterity by his writings, the Italian was the greater of the two in this regard. "Those who are in love with practice without Knowledge," wrote Leonardo, "are like the sailor who gets into a ship without rudder or compass and who never can be certain whither he is going. Practice must always be founded on sound theory. The interpreter of nature is experience; she never deceives us; it is our judgment that sometimes deceives itself, because it looks for effects which experience denies to us." He attacked alchemy and magic with force. "Oh! speculators on perpetual motion, how many vain projects of the like character you have formed! Go and consort with the seekers after gold." "Many have a trade of delusion and false miracles, deceiving the stupid multitude."

To anatomy and physiology Leonardo made many noteworthy contributions. Vasair expressly mentions Leonardo's anatomical studies, having had occasion to examine the manuscript books which refer to them. According to him, Leonardo studied anatomy in the companionship of Marc Antonio della Torre. This learned anatomist taught the science in the Universities, first of Padua and then of Pavia, and at Pavia he and Leonardo may have worked and studied together. We have no clue to any exact dates, but in the year 1506 Marc Antonio della Torre seems to have not yet left Padua. He was scarcely thirty years old when he died in 1512, and his writings on anatomy have not only never been published, but no manuscript copy of them is known to exist. In Leonardo's manuscripts on anatomy, no mention is made of his younger contemporary.

Hunter, the greatest English surgeon of the time of George III, had occasion to examine the anatomical drawings of Leonardo. "I expected," he writes, "to see little more than such designs in anatomy as might be useful to a painter in his own profession. But I saw, and indeed with astonishment, that Leonardo had been a general and a deep student. When I consider what pains he has taken on every part of the body, the superiority of his universal genius, his particular excellence in mechanics and hydraulics, and the attention with which such a man would examine and see objects which he has to draw, I am fully persuaded that Leonardo was the best anatomist at that time in the world. Leonardo was certainly

the first man we know of, who introduced the practice of making anatomical drawings." This opinion has been confirmed by Sir Charles Bell, who stated that "Michael Angelo and Da Vinci were the best anatomists of their day, and therefore, they were the first of artists," and by Robert Knox, who testifies that Leonardo was "one of the greatest of men; the first of all artists—a profound anatomist—inventor of true iconographical anatomy, and perhaps even of the descriptive."

Leonardo, the artist, did not lose opportunity to perform an autopsy when he could. "And this old man, a few hours before his death, told me," he writes, "that he had lived a hundred years, and that he did not feel any bodily ailment other than weakness, and thus while sitting . . . he passed away from his life. And I made an autopsy in order to ascertain the cause of so peaceful a death, and found that it proceeded from weakness through failure of the blood and of the artery that feeds the heart and the other lower membranes, which I found to be very parched and shrunk and withered; and the result of this autopsy I wrote down very carefully and with great ease, for the body was devoid of either fat or moisture, and these form the chief hindrance to the knowledge of its parts. The other autopsy was on a child of two years and here I found everything the contrary to what it was in the case of the old man."

But Leonardo was not a physician. He could draw what he saw, and describe it in script that one could read only by holding it against a mirror—in this way not offending the "faculty." For the medical "faculty" of those days was as coy and timid of new advances as the doe is of the hunter. The congregated college held Aristotle and Galen as infallible individuals. The philosopher had cautioned against just such an eventuality: "I charge you, forever reject those who would expound me, for I cannot expound myself; I charge that there be no theory or school founded out of me; I charge you to leave all free, as I have left all free."

Nevertheless, the teachings of the Stagyrite, with the revival of learning, became canonical, and so it was also with the writings of the Pergamite. In the following extract from the statutes of the Academy at Helmstadt, we observe the spirit of the times:

"We desire the medical art, even as it was rightly and wholly fixed and handed down, under the guidance of God, by the artists Hippocrates, Galen and Avicenna, to be preserved and diffused by teaching. We recommend that . . . all corruptions of medicine not agreeable to the doctrines of Galen and Avicenna, be banished entirely from the Academy."

Galen had written that the thigh bones are curved, that there is an intermaxillary bone, and other absurd statements that the most superficial observation would have proved wrong. Yet Sylvius, the anatomist of the sixteenth century—an able man otherwise—was convinced that Galen was right and all modern experience to the contrary was wrong. Sylvius—who must have been a man devoid of all sense of humor—affirmed that in nature the thigh bones are curved, but their straightness

is due to the narrow trousers that men wore. "A human skeleton was brought to Sylvius. 'Where is this maxillary bone?' he was asked. The faithful Galenist answered angrily, 'Man had this bone when Galen lived. If he has it no longer, it is because sensuality and luxury have deprived him of it.'"¹

In the sixteenth century there lived Andreas Vesalius (1514-1564) of Brussels who revived the study of anatomy from the medical point of view. He looked at the human body, dissected it, and described what he saw, and not what Galen had mistakenly thought he saw. At the age of twenty-two he became Professor of Anatomy in the University of Padua, where his enthusiastic lectures and demonstrations attracted great crowds of students. He audaciously ventured to dissect personally (without the assistance of a barber) human beings, and not only pigs and dogs as had been the custom. He pointed out many of Galen's errors: There *was* marrow in the bones of the hand; the symphysis did *not* separate during parturition; the ascending vena cava did *not* arise from the liver; the mandible was *not* composed of two bones; there was *no* imputrescible bone in the heart; etc. His contributions to our knowledge of the anatomy of the brain, heart, skull, spinal column, ear, pleura, etc., were epoch making. Unlike Leonardo, he could not draw, and he was compelled to employ artists who made the drawings for him. These anatomical investigations and illustrations he gave to the world in his wonderful book, "De Humani Corporis Fabrica."

His passion for dissection of the human body resulted in his undoing. Once he performed an autopsy on a great nobleman, and upon opening the chest, all who were present observed that the heart was still beating. For this act of impiety he was condemned to death, from which he was saved by the king's intervention. His sentence was commuted to making a penance journey to Jerusalem, upon the return from which he was invited to resume the Chair of Anatomy at Padua. On his voyage thither, his ship was wrecked, and he died from hunger and exposure on the shore.

Contemporary with him were the anatomists Cæsalpinus, Eustachius, Fallopius, Servetus, Ingrassias, and Realdus Columbus—men who established the science of anatomy on a foundation of truth and fact, obtained by personal investigation and study. The examination of the structural make-up of man led to further experimentation in the study of the function of the organs, and the discovery of the circulation of the blood.

It had been stated by Galen that the left and right cardiac ventricles were connected by means of openings in the interventricular septum. This Vesalius definitely denied. But he believed with Galen that the arteries contained blood mixed with spirits. The Netherland Anatomist had, however, observed in his study of the finer divisions of the lower vena cava and portal vein in the liver that "the extreme ramifications of these veins inosculate with each other, and in many places appear to unite and be continuous." This statement is the result of a pure anatomical observation, but he drew no general deductions therefrom.

Though Galen knew nothing of the systemic circulation, he surmised, or at least hinted at, a pulmonary circulation. He quite clearly states, "We cannot suppose that any considerable portion of the blood that is sent to the lungs by the former vessel (pulmonary artery) is appropriated by them for nourishment. It is, therefore, evident that it must be transmitted to the left sinus of the heart." To this shrewd guess nothing new had been added for almost fourteen centuries.

To Winter of Andernach, and especially to Servetus, is due the credit for discovering the pulmonary circulation. It is fitting that a few words be written of the life and labors of the latter.

Michael Servetus was born at Tudelle in Navarre in 1511. When fifteen years old, he sought service in Spain under Charles V. He was a deep thinker and a great lover of truth, and there was no place in Spain at that time for such a man. There the cult of the Jesuits were in supreme control, and to offer newer thoughts was considered heretical and to be punished by purification on the auto-da-fé. He, therefore, left the cities of sunny Spain and went to the Protestant countries in search of freedom of self-expression. But the Lutherans and the Calvinists were no less intolerant than were the Papists. Luther himself, for example, derided Copernicus' statement regarding the orbits in which the earth traveled, and he declared, "The fool wants to upset the whole science of astronomy, but as the Holy Scriptures show, Joshua commanded the sun and the moon to stand still and not the earth."

Servetus was very sadly disappointed. He attempted to reform medicinal preparations by writing a book on the rational preparation of syrups. For this attempt at trying to improve on hoary practices, the Parisian Faculty sought to impeach him. One can imagine that if a radical opinion on medicated syrups was deemed deserving of condemnation, how much more would a radical theological opinion arouse the ire of the fanatics.

In 1553, there was published Servetus' book, entitled "Christianismi Restitutio," in which he expressed his doubts regarding the "trinity," "baptism," etc. The Calvinists and Catholics made common cause against Servetus. He was burnt in effigy at Vienna, and when Calvin caught him in his toils in Geneva, he condemned him "to be bound, and led to the place of Champel, there to be fastened to a stake, and burned alive with thy book, as well written by thy hand as printed, even till thy body be reduced to ashes, and thus wilt thou finish thy days, to furnish an example to others who might wish to commit the like." He was executed on October 27, 1553.

In the fifth division of this otherwise uninteresting book—who can now find interest in a theological controversy of the sixteenth century?—we find the passage where reference is made to the pulmonary circulation of the blood.²

"In order properly to understand this condition of things it becomes necessary to know beforehand the substantial generation of the life spirit

itself, which is composed of the inspired air and finest blood, nourished by the same. This life spirit has its origin in the left chamber of the heart, the lungs especially assisting in its generation. It is a delicate spirit breath, produced by the force of warmth, of clear color, burning force and to a certain extent composed of a transparent foam formed out of pure blood and containing in its substance water, air and fire. It is generated by the admixture of the inspired air and the thinned blood furnished by the right chamber of the heart to the left. This, however, does not take place through the middle wall of the heart, as has been hitherto supposed, but by an highly intricate mechanism the finely divided blood is conveyed by the right chamber of the heart by a devious route through the lungs. The lungs prepare it for use by clarifying it and pass it from the arterial vein into the venous artery. It is thus mixed with the inspired air in the venous artery itself and by expiration is again cleansed from soot. Finally the whole mixture is drawn through diastole serving (if I may be permitted to use the expression) as a suitable household utensil for the life spirit.

"That this preparation and assimilation takes place in the lungs, is manifest by the extensive union and anastomosis of the arterial vein with the venous artery of the lung. This is confirmed by the striking size of the arterial vein, which could not have reached such dimensions and have sent the blood from the heart into the lungs with such force by its own nutritive power, nor could the heart serve the lungs in a like manner, especially since in the embryo the lungs receive their nourishment from other sources. . . .

"The lungs also send to the heart not only mere air, but such as is mixed with blood through the venous artery. The admixture, therefore, takes place in the lungs and not in the heart. . . . In the same complicated manner as occurs in the liver, where transmission takes place from the portal vein to the vena cava on the part of the blood, so also happens in the lungs the transfer from the arterial vein to the venous artery on the part of the life spirit."

The discovery of Servetus was plagiarized by Matthew Realdus Columbus, who had obtained possession of one of the few volumes that had not been burnt by Calvin. From his professorial chair at Rome, Columbus taught the pulmonary circulation to his students, and in 1559 he published his book, "*De Re Anatomica*," where we find passages almost identical with those of the martyred physician.

In such theoretical state did William Harvey (1578-1667) find the important question of the blood distribution and circulation. He is one of the great lights of his time which has produced so very many great men. His contemporaries were Shakespeare and Milton, Bacon and Napier, Boyle and Galileo, Spinoza and Descartes, Leeuwenhoek and Malpighi, Mayow and Toricelli. An age that produces such a galaxy of famous men must have in it something that is noble and inspiring.

William Harvey was born at Folkstone, England, in 1578. He was the son of a well-to-do yeoman, much respected in the community where he lived. At nineteen years of age, he graduated from Cambridge University, and then left for the continent, studying in Padua under the great teacher, Fabricius. After four or five years of study in Italy, he returned to England, obtained his doctor's degree in medicine from Cambridge, and began practicing his profession. He was of a choleric and rather impetuous character. "Harvey was not tall," says Aubrey, "but of the lowest stature; round face with a complexion like the wainscot; his eyes, small, round, very black, and full of spirit; his hair, black as a raven, but quite white twenty years before he died; rapid in his utterances, choleric, given to gesture."

There is no doubt that to William Harvey is due the great honor of first describing the circulation of the blood. Cæsalpinus had deductively concluded that the blood must circulate. "The passages of the heart," he wrote, "are so arranged by Nature that from the vena cava a flow takes place into the right ventricle, whence the way is open into the lungs. From the lung, moreover, there is another entrance into the left ventricle of the heart from which then a way is open into the aorta artery, certain membranes being so placed at the mouth of the vessels that they prevent return. Thus there is a sort of perpetual movement from the vena cava through the heart and lungs into the aorta artery." Cæsalpinus' conceptions were based, however, not on experimentation, and he did not explain how the arteries and veins are connected.

Fabricius, the teacher of Harvey, had pointed out that the veins had "little doors" or valves to prevent the return flow of the blood to the heart. All these facts must have been known to Harvey.

"When I first gave my mind to vivisection," wrote Harvey, "as a means of discovering the motions and uses of the heart, and sought to discover these from actual inspection, and not from the writings of others, I found the task so truly arduous, so full of difficulties, that I was almost tempted to think . . . that the motion of the heart was only to be comprehended by God. . . . At length, and by using greater and daily diligence and investigation . . . making frequent inspection of many and various animals, and collating numerous observations, I thought that I had attained the truth . . . and that I had discovered . . . both the motion and the use of the heart and the arteries."

In 1616, Harvey in his Lumleian lecture first expounded his discovery of the circulation of the blood. He waited twelve years, until 1628, before he presented his work to the world in that great classic, "The Movement of the Heart and the Blood."

In Chapter IX of his book, he thus describes the motion of the blood:

"First: the blood is incessantly transmitted by the action of the heart from the vena cava to the arteries in such quantities that it cannot be supplied from the ingesta, and in such a manner that the whole must

very quickly pass through the organ. Second: the blood under the influence of the arterial pulse enters, and is impelled in a continuous, equable and incessant stream through every part and member of the body, in much larger quantity than were sufficient for nutrition, or than the whole mass of fluids can supply. Third: the veins in like manner return the blood incessantly to the heart from all parts and members of the body. These points proved, I conceive it will be manifest that the blood circulates, revolves, propelled and then returning, from the heart to the extremities, and thus that it performs a kind of circular motion."

Of course, Harvey met with much abuse and ridicule and skepticism. The French school raised absurd objections. First of all, the theory emanated from an Englishman (the historic enemy of the French); that alone was enough to condemn it. Secondly it controverted the time-honored laws of Hippocrates and Aristotle and Galen. And thirdly, "If the blood circulates," said they, "it is useless to bleed, because the loss sustained by an organ will be immediately repaired, hence bleeding would be useless, therefore the blood does not circulate." Even in England, Reid, the lecturer on anatomy, continued teaching the Galenic theories for thirty years after Harvey's book was published. And not only did Harvey meet with scientific disapproval, but the public and the medical profession, thinking that he was "crackbrained," shunned him, so that "he fell mightily in his practice."³

In 1651, Jean Pecquet discovered the thoracic duct, and described the lymphatic circulation. Four years after Harvey's death, Malpighi (1628-1694), in 1661, described the capillary circulation. He wrote, "There appears a network made up of the continuations of the two vessels. This network not only occupies the whole area, but extends to the walls, and is attached to the outgoing vessel. . . . Hence it was clear to the senses that the blood flowed along tortuous vessels, and was not poured into spaces, but was always contained within tubules."

Harvey once wrote in an album "*Dii laboribus omnia vendunt.*" With labor and patience men have wrested from Nature many of her secrets, and are daily delving deeper, making themselves more adept in their procedures of investigation, and more deft in their technic.

In the first half of the seventeenth century, the force of Francis Bacon's teachings began to bear fruit. He was the great preacher of research and experimentation. "Man," he wrote, ". . . can do and understand so much, only as he observes in fact or in thought of the course of nature; beyond this he neither knows anything, nor can do anything." "Of such observation there will be hardly any . . . proficience . . . except there be some allowance for . . . experiment." "For Nature like a witness reveals her secrets when put to torture." He preached united effort, and his influence resulted in the establishment of the learned scientific societies in Europe. In the "House of Solomon," Bacon imagined a Utopian learned society. The "riches" of the House

of Solomon consisted in a series of laboratories devoted to all conceivable subjects of experimental research, with facilities of Utopian perfection—laboratories beneath the ground, observations on high towers upon mountain peaks; all apparatus for physiological experiments; botanical and zoölogical experiment stations in the fullest sense of the word; places for dissection, chemical, pharmacological and physical laboratories; special laboratories for the study of heat, of optics, of sound, of engineering problems, all sketched in a completeness which the twentieth century has not reached, but along lines toward which scientific progress has been advancing. All this is put in charge of a hierarchy of scientists, the Merchants of Light, who are to bring news from foreign lands, the Depredators who ransack books for scientific facts, the Mystery Men who collect experiments in the mechanical arts, the Pioneers who try new experiments, the Compilers who tabulate the results, the Dowsy Men who try to derive practical benefit, the Lamps who direct new experiments, the Inoculators who try these, the Interpreters of Nature who “raise . . . discoveries into greater observations, axioms, aphorisms.”⁴

In Italy was organized the first scientific society, the *Accademia del Cimento* of Florence (1657–1667). The Royal Society of England was organized during the years 1660 to 1662. In France, the *Académie des Sciences* was established in 1666. These learned societies encouraged research, corresponded with one another, so that they spread their discoveries, and by grants aided investigators in different lands in the pursuit of their experimentation.

It had been long the aim of certain men to find means to aid the sense of vision, so as to be in a position to examine the minute in Nature. They say that Roger Bacon first ground glasses for the eyes. It was either Galileo or Fontana or Jansens who first devised the microscope—in very crude form—and it was Drebbel of Holland who improved it early in the seventeenth century.

In 1665, the great Englishman, Robert Hooke (1635–1703), published his book on “*Micrographia*,” in which he describes certain minute forms that he had observed by means of the microscope. “In every little particle of matter,” he exclaimed, “we behold almost as great a variety of creatures as we are able before to reckon in the universe,” and he urged further study. “We have imperfect senses,” he wrote, “and imperfect memories, hence imperfect understanding; only the experimental knowledge can rectify these defects.”

Hooke was followed by the great investigators, Malpighi and Swammerdam and Leeuwenhoek, who made such very wonderful discoveries by means of the microscope, and who were the true founders of our modern conceptions of various biological sciences.

Marcello Malpighi was born near Bologna in Italy, in 1628. He studied in the University of that city, and in 1653 he obtained the medical doctorate degree. At Bologna and later at Pisa he held the Chair of Anatomy, was personal physician to Pope Innocent XII, and was

honorary member of many foreign societies. His histological work on the lungs, demonstrating the "air cells," on the passage of the blood through the capillaries, on the histology of the glands, skin, etc., are epochal. He also studied the anatomy of the silk worm, and made fine drawings descriptive of what he saw. In studying plants, he saw the cells, which he called "utricles," thus anticipating the discovery of Schleiden and Schwann.

Contemporaneously there lived in Holland, Jan Swammerdam (1637-1680), whose industry, knowledge and skill resulted in the addition of much to our knowledge of biology. In his book, "*Biblia Naturæ*," where all his writings are collected, we find the results of his study of insects. It "contains about a dozen life histories of insects worked out in more or less detail. Of these that of the mayfly is the most famous, that on the honey bee the most elaborate." He showed experimentally that nerves are irritable, and that muscles may respond to stimuli after their removal from the body. "It is evident," he writes, "from the foregoing observation, that a great number of things concur in the contraction of the muscles, and that one should be thoroughly acquainted with that wonderful machine, our body, and the elements with which we are surrounded, to describe exactly one single muscle and explain its action. On this occasion it would be necessary for us to consider the atmosphere, the nature of our food, the brain, marrow and nerves, that most subtle matter which instantaneously flows to the fibers, and many other things, before we could expect to attain a sight of the perfect and certain truth."

We must not forget to mention that it was Swammerdam who took a decided stand against the supposition that small living things may be created spontaneously—but it remained for Pasteur, two hundred years later, definitely to demonstrate the absurdity of the conception of the spontaneous generation of life.

With Antony van Leeuwenhoek (1632-1723) began systematic microscopic anatomy. He was a very quiet and composed man, who lived to a very great age. Of him Richardson writes, "In the face peering through the big wig there is the quiet force of Cromwell and the delicate disdain of Spinoza. . . . It is a mixed racial type, Semitic and Teutonic, a Jewish Saxon; obstinate and yet imaginative; its very obstinacy a virtue, saving it from flying too far wild by its imagination."⁵

Leeuwenhoek was the son of a rich Delft brewer, and while young was trained in anything but scientific occupations. But the wealth of the family gave him influence and power, and after dropping the commercial pursuits, for which he seemed to have no taste, he began scientific investigations. He knew the famous scientists of his day. In 1673, De Graef sent his first paper to the Royal Society of London. In 1698, his fame had grown so great, that Peter the Great of Russia visited him to inspect his microscopes.

Leeuwenhoek was neither trained in medicine, nor was he a practitioner. He was skeptical of medicine as a practical art. When he did venture into a medical research, he did so half apologetically. "Some will think," he writes, "that I am going out of my province, but these considerations weigh very little with me, forasmuch as every judicious person knows that physicians themselves in many things proceed merely by guess, and, therefore, I assume to myself the liberty of offering my suggestions on the subject." The subject was the physiology of digestion.

In his essay, "On the Circulation of the Blood," he reports that the blood is composed of exceedingly small particles, named globules, which in most animals are of a red color, swimming in a liquid, called by physicians the serum. By watching the globules, one observed the motion of the blood. When he examined the tail of the tadpole, he was delighted to see the capillary circulation. "A sight presented itself more delightful than any mine eyes had ever beheld; for here I discovered more than fifty circulations of the blood in different places, while the animal lay quiet in the water, and I could bring it before my microscope to my wish. For I saw, not only that the blood in many places was conveyed through exceedingly minute vessels, from the middle of the tail towards the edges, but that each of these vessels had a curve or turning, and carried the blood back towards the middle of the tail, in order to be again conveyed toward the heart. Hereby it plainly appeared to me that the blood-vessels I now saw in this animal and which bear the name of arteries and veins, are, in fact, one and the same; that is to say, that they are properly termed arteries so long as they convey the blood to the furthest extremities of its vessels, and veins when they bring it back to the heart. And thus it appears that an artery and vein are one and the same vessel prolonged or extended."

The great revolutionary practitioner of the sixteenth century was Philip Theophrastus Bombast Paracelsus von Hohenheim (1493-1541). He was born in Switzerland. His father was the illegitimate son of a high nobleman. In his youth he had to struggle with poverty and want. He received his medical education from his father, and he never studied in a university, for which he was much criticised as well as for his independent thinking. "My accusers," he remarks, "complain that I have not entered the temple of knowledge through the legitimate door. But which is the truly legitimate door? Galen and Avicenna, or Nature? I have entered through the door of Nature: her light and not the lamp of an apothecary's shop has illuminated my way."

Says Robinson: "Paracelsus was an iconoclast: he had no use for the medicine of his day. His aim was to reform it from beginning to end. He was not the highest type of reformer. He had not the calm dignity and lofty reserve of Giordano Bruno, he lacked the sublimity of Spinoza, and the modesty of Darwin was not his. He had a streak of clownishness in him and possessed the elements of a buffoon. He was often as gross as the autocrats of his time, and could have engaged in

and meekness pleased the orthodox practitioners, and they withdrew their open opposition to the book.

The faculty in the time of Louis XIV was the same in aspirations and ideas as the faculty of the time of the last Valois. Surgery was held in contempt, because no dignified physician would hold a knife in his hand, and to elevate the barber to the rank of a doctor was not to be thought of. The faculty opposed innovation. As has been stated, circulation of the blood was rejected because Harvey was an Englishman. If the blood did circulate it was against the laws of the faculty. It had no business to flow contrary to the beliefs of Hippocrates and Galen. The prescribing of antimony was prohibited by the Parisian School, for the simple reason that the faculty of Montpellier recommended it. De Mauvillain espoused the cause of antimony and of circulation of the blood and was, therefore, ostracized from the association of physicians.

As strict partisans of the principles of the Parisian faculty, Jean Riolan (1577-1657) and Guy Patin (1601-1672) stand preëminent. Patin, "polemical medical writer and clever humorist of that day," said of Riolan that he would rather give up a friend than an assertion. They were strict adherents of the Iatro-chemical school, founded by Sylvius, "which like other systems might rather be called a systemic phantasy." This system is based upon the elements of chemistry—the improved successor of alchemy and the first step towards true chemistry; upon the new knowledge of the circulation of the blood; and upon the closer acquaintance with the chyle and lymph vessels (which had been acquired in this period), as well as upon the old doctrine of the "*spiritus and calor innatus*" of the heart. His system, although its author always professes to accept only "experience by means of the senses, is constructed far less upon experience than upon false conclusions drawn from experimental observation, whose connection with his theory is on the whole arbitrary and forced." (Baas.)

Opposed to their beliefs were the theories of the Iatro-mathematical School whose motto was "In your practice concern not yourselves with theories." The originator of this system was Santorio Santoro (1561-1636), professor in Padua and Venice. Their idea was to treat all diseases with precision, and that all functions of the body were rather physical than chemical. "Thus digestion was referred to as a process of mechanical trituration, and the absorption of chyme was explained as due to the pressure arising from the action of the intestinal movements upon the comminuted food. In a similar way the secretions were referred to as the resistance created by the corners, angles, curves, etc., of the vascular system, and so on."

Guy Patin was a learned man, a brilliant writer, and thoroughly acquainted with the Latin language, which he wrote to perfection. "His creed contained two articles—bleeding and purging with senna." Certainly he was not a quack, but with the intolerance of his time, he was antagonistic to all who were against the existing order of things. It

might have been of him that Molière has said—"that a dead man is only a dead man, and is of no consequence, but a neglected formality does great harm to the entire profession." Guy Patin strongly believed "in having his patient die according to rule rather than survive in violation of it."

In "Le Medecin Volant" we find Molière's first attack on medicine. Sganarelle, the famous rogue, undertakes to impersonate a dignified physician, in order to aid his master in his love affair. He assumes the doctor's gown and talks with the pedantic air characteristic of the physician:

"Hippocrates says, and Galen, by undoubted arguments, demonstrates that a person is not in good health when he is ill. You are wise to place all your hope in me; for I am the greatest, the noblest, the most learned physician in vegetable, sensitive and mineral faculty."

Upon being told that his patient is dying, Sganarelle exclaims:

"Ah! let her be careful not to do so; she must not amuse herself by allowing herself to die without a prescription from the doctor."

Doctors stood very much on ceremony in those days. In one of the farces of Molière, a doctor rebukes a patient who was too abrupt in his address:

"You must be very ill bred, very loutish and very badly taught, to speak to me in that fashion, without first taking off your hat, without observing *rationem loci, temporis et personae*. What! You begin by an abrupt speech, instead of saying, *Salve, vel salvus sis, doctor doctorum cruditissime*. What do you take me for, eh?"

In "Le Mariage Forcé," Molière throws a shaft at the University of Paris, which was endeavoring to persuade Parliament to confirm a sentence dated September 4, 1624, which condemned to death all those who would dare to attack the Aristotelian doctrine.

Sganarelle meets two philosophers discussing and quarreling. He accosts one and is met with gibberish that he does not understand. "Devil take the scholars," he exclaims, "they will never listen to anybody. I see it was the truth I was told that this Master Aristotle was a talker and nothing else."

The doctor has a very good opinion of himself:

"Get along, you are more impertinent than the fellow who maintained that we ought to say the *form* of a hat instead of the *figure*, and I will prove it to you at this time, by the help of demonstrative and convincing reasons, and by arguments *in Barbara*, that you are and never will be anything but a simpleton and that I am and ever shall be, *in utroque jure*, the Doctor Panrace . . . a man of sufficiency, a man

of capacity, a man finished in all the sciences, natural, moral and political. A *savant*, *savantissime*, *per omnes modos et casus*. A man who has a knowledge superlative of fables, mythologies and histories; grammar, poetry, rhetoric, dialectics and sophistry; mathematics, arithmetic, optics, ornieritics, physics and metaphysics; cosmometry, geometry, architecture, specular and speculative sciences, medicine, astronomy, astrology, physiognomy, meteposecopy, chromancy, geomancy."

In that hugely comical farce, "Monsieur de Pourceaugnac," the hero is falsely accused of being insane, and the physicians are convinced of the truth of the accusation, because the patient does not take to it kindly that they doubt his mental equilibrium. After the senior physician has given a very lengthy and very laughingly learned discussion of the case, the junior doctor, in rapt admiration, replies:

"Heaven forbid, Sir, that it should enter my thoughts to add anything to what you have just been saying. You have discoursed too well on all the signs, symptoms and causes of this gentleman's disease. The arguments you have used are so learned and so delicate that it is impossible that he is not insane and hypochondriacally melancholic; or were he not so, that he ought to become so, because of the beauty of the things you have spoken and of the justness of your reasoning. Yes, Sir, you have graphically depicted, *graphice depinxisti*, everything that appertains to this disease. Nothing can be more learnedly, judiciously and ingeniously conceived, thought, imagined than that you have delivered on the subject of this disease either as regards the diagnostic, the prognostic, or the therapeutic, and nothing remains for me to do but to congratulate this gentleman upon falling into your hands. All I should like to add is to let all his bleedings and purgings be of an odd number, *numero duos in pare gaudet*, to take the whey before the bath, and to make him a forehead plaster, in the composition of which there should be salt—salt is the symbol of wisdom."

In the "Imaginary Invalid," the father of a young doctor praises his son in the following words:

"In all disputations has he rendered himself formidable, and no debate passes but he argues loudly and to the last extreme on the opposite side. He is firm in dispute, strong as a Turk in his principles, never changes his opinion, and pursues an argument to the last recesses of logic. . . . But, above all, what pleases me most is his blind attachment to the principles of the ancients, and that he would never listen to the pretended discoveries of our century concerning circulation of the blood and other opinions of the same stamp."

Once, M. Argan, the imaginary invalid, refuses to take a prescription of his physician. The latter does not seem to be at all pleased about it:

"What daring boldness; what a strange revolt of a patient against his doctor! . . . A clyster which I have had the pleasure of composing

myself, invented and made up according to all the rules of the art. . . .
A case of high treason against the faculty!"

It is in this state that medicine remained during the eighteenth century.

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CHAPTER IV

HISTORY OF EIGHTEENTH CENTURY MEDICINE

By C. W. G. ROHRER, M.A., Ph.D., M.D.

Anatomy and physiology, p. 50—Embryology and comparative anatomy, p. 56—Chemistry, general and physiological, p. 57—Pathology and bacteriology, p. 58—Materia medica and therapeutics, p. 62—The practice of medicine, p. 66—Surgery, general and operative, p. 72—Gynecology and obstetrics, p. 73—Hygiene and preventive medicine, p. 74—The diseases of the eye and ear, p. 77.

There is scarcely a period in the history of medicine fraught with greater interest than that embraced by a full import of the above title. It is true, the archives of the eighteenth century are not intercalated by many such epoch-making contributions to medical science and art as the discovery of the circulation of the blood, of anesthesia, of antiseptis, and other similar and important innovations afforded; nor could it be said that it can justly boast of having been the "greatest of centuries," an appellation not inaptly applied by Dr. James J. Walsh * to the thirteenth century. But, withal—

"Our little systems have their day;
They have their day and cease to be;"

and the discovery of vaccination by Jenner, towards the close of the eighteenth century, above all other achievements and advancements, renders its place secure for all time in the annals of medicine.

Eighteenth century medicine, in point of time extending from 1700 to 1799, both years included, was dominated by theories and systems, by cults and creeds. Nevertheless, this era was productive of numerous beneficial and lasting reforms in the healing art. Quackery and superstition were gradually being eliminated from medical practice; the royal touch was fast losing its therapeutic efficacy; and witchcraft and astrology were slowly but surely giving way to more humane and more rational explanations as to the theory and causation of disease. The increasing popularity of male obstetricians, the far-reaching influence of practical anatomy and pathology as promulgated by the two Hunters, by Baillie, and by Morgagni, and the founding of numerous hospitals, and medical and scientific bodies throughout England, on the Continent, and in America, all conspired to make the eighteenth century one well worthy of serious consideration by medical historians. In brief,

* "The Thirteenth, the Greatest of Centuries," by James J. Walsh, M.D., Ph.D., LL.D., New York, 1907.

the impress which it has made upon the art of healing, and the inestimable boon conferred upon humanity by the inventions and discoveries appertaining thereto, assign to this century a position of no common merit upon the scroll of fame.

There are several ways in which this subject might be judiciously and satisfactorily treated. In a concise monograph, however, designed especially for the already overworked medical student, his needs and his requirements should be primarily borne in mind. As his work is apportioned to him by subjects conforming to a standard curriculum, an adherence to such a plan in the present essay will doubtless be beneficial and at the same time facilitate a ready reference to whatever topic he may have in hand. Therefore, I shall discuss the salient points of each of the principal branches of medical study * under the following ten subheadings, endeavoring, as far as is possible, to arrange my data in chronological order:

- I. Anatomy and Physiology.
- II. Embryology and Comparative Anatomy.
- III. Chemistry, General and Physiological.
- IV. Pathology and Bacteriology.
- V. Materia Medica and Therapeutics.
- VI. The Practice of Medicine.
- VII. Surgery, General and Operative.
- VIII. Gynecology and Obstetrics.
- IX. Hygiene and Preventive Medicine.
- X. The Diseases of the Eye and Ear.

Some of the branches of medicine enumerated above, at the time of which I write, were only in the formative stage, scarcely meriting a separate consideration. Then, too, a number of important medical discoveries bind the closing years of the seventeenth century with the opening years of the eighteenth; and, in a corresponding manner, the eighteenth and the nineteenth centuries are inseparably blended, no distinct hiatus existing between them. The leading medical characters of the day also belong to no circumscribed age or period, their influence permeating for good the Æsculapian art of all time.

I. ANATOMY AND PHYSIOLOGY

Identified with the progress of improvement in anatomy, in the eighteenth century, we find such familiar names as the two Hunters, the three Monros, Douglas, Cheselden, Scarpa, Winslow, and a host of other workers and investigators. Among the earliest and most successful cultivators of anatomy during this century was James Douglas (1675-

* The designation, "medical study," is here used advisedly, because the great work of which this essay forms but an integral part being essentially medical in character, it behooves us not to go very far afield into the history of surgery, other than in its direct bearing upon the subject matter treated in the text.



William Hunter.

FIG. 1.—WILLIAM HUNTER (1718-1783)

A famous British physician, obstetrician and founder of the Great Windmill
Street school of anatomy

1742), the predecessor of the distinguished William Hunter as a teacher of anatomy in London. In 1707 Douglas published his specimen of "Comparative Anatomy,"¹ containing the most correct account of the muscles which had yet appeared, and giving a comparative description of all the muscles in a man and in a dog. In 1715 appeared his specimen of "Anatomical Bibliography,"² in which he gave an account of the several works upon anatomy, with biographical sketches of the writers. Douglas, however, is best known to the medical student by his publication on the subject of the peritoneum, a portion of which constitutes the posterior (recto-uterine) ligament of the uterus, forming a pouch called Douglas's cul-de-sac, or space.

William Cheselden (1688-1752), who early distinguished himself by his proficiency in anatomy, which he had studied under Cowper, became in 1711, at the age of only twenty-two, a public lecturer on anatomy and surgery. In 1713, he published his "Anatomy,"³ accompanied by some select cases in surgery, and a syllabus of his lectures. This work acquired great popularity, rapidly passing through six editions. To the fourth, and all the succeeding editions, he subjoined, in an appendix, a short account of the operation of lithotomy. In 1718 he became surgeon to St. Thomas's Hospital; and in 1733 his "Atlas of Osteology" was published.

Contemporary with Cheselden was Laurence Heister (1683-1758), a celebrated German physician, surgeon, anatomist and botanist, whose "Compendium of Anatomy,"⁴ his most distinguished work, was first published in 1717. It became a very popular book, and went through a great number of editions. It is valuable, both for its conciseness and clearness, as a physiological as well as anatomical textbook. His "Institutions of Surgery,"⁵ published in the German, in 1718, was soon translated into Latin, and most of the modern languages of Europe.

The great center of anatomic teaching, at the beginning of the eighteenth century, was Paris. The situation, however, was soon changed, the city of Edinburgh coming into prominence, later ranking as one of the leading medical centers of the world. This transformation was chiefly effected, in the first instance, by the splendid talents and unrivaled exertions of Alexander Monro, the first (1697-1767). His father, John Monro, a surgeon in King William's army, settled in Edinburgh, in 1700. Perceiving his son's early indications of genius and strong inclination for medicine, he carefully superintended his early education and afterwards sent him to London to study anatomy under Cheselden. Monro was a diligent student, devoting himself with the utmost assiduity to dissection, and the preparation of anatomical specimens, which he sent home. From London he proceeded to Paris, and thence, in the autumn of 1718, to Leyden, where Boerhaave was at that period the mighty magnet of attraction. Returning to Edinburgh in 1719, he was duly examined and qualified by the Surgeon's Guild; and, in 1720, on recommendation of the Town Council, he was elected professor of anatomy in the newly-established university, at the age of twenty-two years. In point of service, his career as a teacher and investigator is

without precedent in medical annals. In verification of this statement, I wish to quote the following splendid tribute to his worth, and record of his achievements, from Garrison's "History of Medicine":⁶

"Being a teacher of marked ability, his courses were soon followed by enthusiastic students in large numbers, the roster climbing from 57, in 1720, to 182, in 1749, this steady arithmetic progression being interrupted only by the Rebellion of '45. Alexander Monro followed his father's plan for his own son, and the latter extended the same policy to the grandson, both of whom were also named Alexander, so that the three Monros, *primus*, *secundus*, and *tertius*, as they were called, held the chair of anatomy at Edinburgh in uninterrupted succession, like some entailed estate, for a period of one hundred and twenty-six years (1720-1846). The men of the Monro dynasty were, all of them, original characters of unusual attainments, authors of many valuable works, morbid on the subject of controversy, it is true, but in every way worthy of the confidence placed in them by their fellow-townsmen. During the period 1720-90, some 12,800 students were taught by Monro *primus* and *secundus* alone, and it was largely due to them that Edinburgh became the great center of medical teaching that it was in the 'last century.' "

Another remarkable family of anatomists, Prussians by birth, were the Meckels, father, son and two grandsons. Johann Friedrich Meckel, the elder (1724-74), of Wetzlar, graduated at Göttingen with his noteworthy dissertation on the fifth nerve (the sphenopalatine or Meckel's ganglion) in 1748, and became professor of anatomy, botany, and obstetrics at Berlin in 1751. He was the first to describe (also in 1748) the submaxillary ganglion. His son, Philipp Friedrich Theodor Meckel (1756-1803), of Berlin, graduated at Strassburg in 1777, with an important dissertation on the internal ear. He became professor of anatomy and surgery at Halle in 1779. His son, Johann Friedrich Meckel (1781-1833), of Halle, called the younger Meckel, published his work on normal human anatomy in 1815, and is memorable as the discoverer of the Meckel diverticulum of the small intestines.

Antonio Scarpa (1747-1832), a brilliant Venetian, discovered the membranous labyrinth of the ear, the nasopalatine nerve, and the triangular space in the upper third of the thigh, called Scarpa's triangle. His name is also identified with a pair of canals in the palate process of the superior maxillary bone, termed the foramina of Scarpa.

William Hunter (1718-1783), of Scotch parentage, originally a theological student, and a pupil of Cullen, went to London in 1741, began to lecture on anatomy and surgery in 1746, and soon acquired a great reputation as a surgeon, obstetrician, and anatomist. In 1768, he built the famous anatomic theater and museum in Great Windmill Street, laboring here to the end of his days. At this school the best anatomists and surgeons of the period, including his brother John, were trained. His greatest work, "On the Anatomy of the Human Gravid Uterus,"

published in 1774, was the outcome of thirty years of strenuous toil: and his two lectures on the history of anatomy, delivered in 1784, are models of their kind.

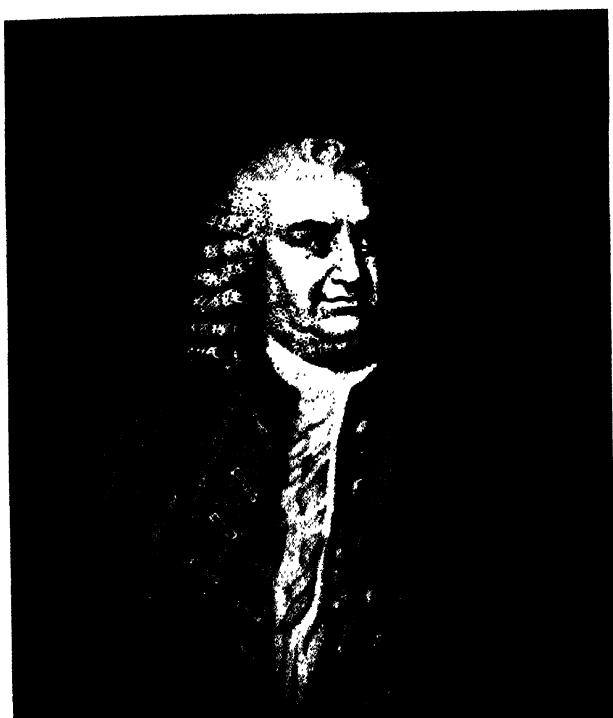
William Cruikshank (1745-1800), of Edinburgh, a celebrated anatomist, for many years filled the post of librarian to William Hunter and afterwards became his assistant lecturer, published, in 1786, his "Anatomy of the Absorbents,"⁷ in which he described the structure and situation of the valvular lymphatic absorbents. This paper, the most correct and valuable which we have upon the subject, embodies the results of his labors with William Hunter.

Towards the end of the century, Samuel Thomas von Soemmerring (1755-1830), a native of Western Prussia, now best remembered by his classification of the cranial nerves, wrote a monumental treatise on anatomy. Two of the four volumes comprising John Bell's excellent system of "Anatomy"⁸ also belong to the eighteenth century, of which the first was published in 1793, and the second in 1797.

Of the physiologists of the eighteenth century, some four or five names overshadow all others. These are: Haller, Hales, Réaumur, Spallanzani and Hewson. Albrecht von Haller (1708-1777), a disciple of Boerhaave, is sometimes called the "Father of Modern Physiology." He was a laborious student and painstaking investigator, surpassing even Boerhaave himself in the extent and diversity of his information. He was more profoundly acquainted with the literature and biography of medicine than any other man living before or since. Having graduated at Leyden, he accepted the professorships of Medicine, Anatomy, Botany and Surgery in the University of Göttingen, then just founded by George II, as elector of Hanover. Here he remained for seventeen years, incidentally doing his best experimental work. His pen was never idle and during this time he composed no fewer than eighty-six books and twelve thousand reviews of books, besides poetry and historic novels. In 1743 he commenced the publication of a series of "Anatomical Plates," amounting in all to thirty-six. The first edition of his excellent "Manual of Physiology"⁹ appeared in 1747, and was eagerly sought after, passing rapidly through many editions and translations. Twelve years later, in 1759, he published the first volume of his great work on physiology,¹⁰ consisting of eight quarto volumes, the whole of which was not given to the world till 1766, eleven years before the death of the author.

Ranking next to Haller's, in eighteenth century physiology, is the name of Stephen Hales (1677-1761), an English clergyman remembered as the originator of artificial ventilation, and for his pioneer work (his most important) on the mechanical relations of blood-pressure.

René-A.-F. de Réaumur (1683-1757), in a series of experiments upon a pet kite, performed in 1752, succeeded in isolating the gastric juice and demonstrating its solvent effect upon foods,¹¹ thereby materially advancing the physiology of digestion. Abbate Lazaro Spallanzani (1729-1799), an astute Italian observer, confirmed and extended Réaumur's results. Spallanzani discovered the digestive power of saliva, and reaf-



Im neuen Sammler, der sich findet
Haller *Wien 28/A 1777*

FIG. 2.—ALBRECHT VON HALLER (1708-1777)

A distinguished Swiss physiologist, anatomist, botanist and poet

firmed the solvent power of the gastric juice,¹² failing, however, to recognize its acid character.

William Hewson (1739-1774), an English physiologist of note and a pupil of the Hunters, achieved distinction through his work on the lymphatics and on the coagulation of the blood. Hewson's discovery of the lacteal and lymphatic vessels in birds, reptiles, and fishes attracted much attention at the time; and the publication of his memoir on this subject won for him the Copley medal in 1769, and in 1770 he was further honored by being elected a Fellow of the Royal Society.

II. EMBRYOLOGY AND COMPARATIVE ANATOMY

In the eighteenth century much work was done in comparative anatomy, but embryology as a distinct branch of medical science had received but scant attention. Caspar Friedrich Wolff (1733-1794), of Berlin, the founder of modern embryology, was one of the most original spirits of his time. This science dates from the publication, in 1759, of Wolff's great work, the "*Theoria Generationis*." Though his ideas were discredited for sixty years through the influence of Haller, they began to gain ground in 1812, when the younger Meckel translated his great monograph on the development of the intestines in the chick (1768-69). His teachings were then followed up by such investigators as Oken, Meckel, Tiedemann, and Panda; and after them, by von Baer, now regarded as the greatest among modern embryologists. Wolff's memoir on the development of the intestines in the chick, one of the acknowledged classics of embryology, is described by von Baer as "the greatest masterpiece of scientific observation that we possess." His name was immortalized by his discovery of the Wolffian bodies.

Among the comparative anatomists of the eighteenth century we find the names of James Douglas, John Hunter, Felix Vicq d'Azyr, Johann Friedrich Blumenbach, John Barclay, Peter Camper, and a host of others. The works of James Douglas have already been mentioned. John Hunter,¹³ especially distinguished as a surgeon and physiologist, formed a museum which contained 13,682 specimens, a large number of which were comparative anatomy specimens.* Vicq d'Azyr (1748-1749), permanent secretary of the Paris Academy of Medicine, was the greatest comparative anatomist of the French school of the eighteenth century. Blumenbach (1752-1840), and Camper (1722-1789), were the founders of anthropology and craniology. The latter, in 1760, introduced the "facial angle" as a criterion of race. John Barclay (1758-1826), of Edinburgh, formed a collection containing a total of 2,512 preparations of which 1,457 were comparative anatomy specimens.

* In 1861 the scientific works of John Hunter were published, in two octavo volumes, under the caption "*Essays and Observations on Natural History, Anatomy, Physiology, Psychology, and Geology*." These were edited by Professor Richard Owen. Vol. I contains observations on natural history, physiology, palæontology, phytology, and a treatise on animals. Vol. II contains the observations on comparative anatomy.

Several years before his death, Barclay presented his collection to the Royal College of Surgeons of Edinburgh, where they now constitute the Barcleian Museum.

III. CHEMISTRY, GENERAL AND PHYSIOLOGICAL

Chemistry, a most important branch of natural science, especially as auxiliary to the practice of medicine, received many notable advancements in the eighteenth century. Chief among these should be mentioned the influence exerted upon the theory of respiration by the discovery of the four principal gaseous constituents of the atmosphere, viz., carbon dioxid by Black (1757), hydrogen by Cavendish (1766), nitrogen by Rutherford (1772), oxygen by Priestley and Scheele (1771), and Lavoisier (1775). The experiments made upon the physiology of digestion, with especial reference to the solvent property of the gastric juice and the digestive power of the saliva, while not strictly of an analytical nature, had their bearing upon the progress of chemistry.

Johann Joachim Becker (1635-1682), and Georg Ernst Stahl (1660-1734), were the first to develop the theory of chemical action and the constitution of compounds, thus dissipating the belief previously advanced by Robert Boyle (1627-1691) that there existed a "first matter," parts of which differed from one another only in certain qualities or accidents. They (Becker and Stahl) enumerated as the four primal elements: water, air, earth, and phlogiston, or the essence of fire; and, curiously enough, their deductions seemed to account very fairly for the various changes in bodies.

Sir Isaac Newton (1642-1727), an English mathematician and discoverer of the law of universal gravitation, likewise contributed his researches in regard to the nature of gases and the method of generating them. He taught that dense bodies were rarefied into the several kinds of air by the process of fermentation. He also further observed that the atmosphere contained particles of different nature, by which it was fitted to be the "breath of life" to vegetables and animals.

Modern chemistry, however, may be said to have had its beginning with the work of Stephen Hales (1677-1761), an English clergyman possessed of an inventive turn of mind, who, early in the eighteenth century, began his important study of the elasticity of air. Hales, it should be stated, was the originator of artificial ventilation (1743); he having previously, in 1733, enriched physiology by performing important experiments on the mechanical relations of blood-pressure. The real significance of his work, however, lies in the fact that it gave impetus to the investigation of the properties of gases by such chemists as Black, Priestley, Cavendish, and Lavoisier.

Hales' careful studies were continued by a younger confrère, Joseph Black (1728-1799), whose experiments in the weights of gases and other chemicals constituted the first steps in quantitative chemistry. Black was of Scotch descent, having been a friend and pupil of Dr. William

Cullen, at the University of Glasgow, under whose instruction he acquired a superior skill in chemical manipulation. In 1757, within three years after completing his medical course, he made the discovery of the properties of carbonic acid, which he called by the name of "fixed air." He also evolved the theory of "latent heat," which opened the way for James Watt's improvements in the steam engine.

Joseph Priestley (1733-1804) was the next contributor to chemical knowledge. He was a celebrated English clergyman and natural philosopher, having been born in Yorkshire, near Leeds. He was noted for his general experiments with gases, and in particular for his discovery of oxygen, or as he named it, "dephlogisticated air."

Henry Cavendish (1731-1810), a pupil of Dr. James Black, discovered the composition of many substances, notably of nitric acid and of water.

Antoine Laurent Lavoisier (1743-1794), the eminent French chemist, can justly be called the "founder of modern chemistry." Lavoisier discovered the true nature of the interchange of gases in the lungs, and overthrew the phlogiston theory by his introduction of quantitative relations in chemistry. He proved that inspired air is converted into Black's carbonic acid or "fixed air," the nitrogen or "azote" alone remaining unchanged.

IV. PATHOLOGY AND BACTERIOLOGY

A good physician must, of necessity, be a good pathologist; and the same remark is applicable to the surgeon. Pathology—that branch of medicine whose object is the knowledge of disease—was cultivated with assiduity in the eighteenth century. Already in 1679 the "*Sepulchretum*" of Theophilus Bonet (1620-1689),¹⁴ containing all the postmortems of the sixteenth and seventeenth centuries, was issued. It is an enormous compilation, and constitutes a new era in the history of pathological anatomy. Prior to the publication of the "*Sepulchretum*," a great number of physicians had devoted themselves attentively to necropsy, and by their labors a considerable quantity of materials was collected. These materials, novel and in a great measure unique by reason of their striking originality, were capable of shedding a bright light on the seat and nature of a certain number of diseases; but, unfortunately, they were lost in a multitude of volumes. In order to become beneficial to science it was necessary to collect, examine, and classify them according to their analogies, to deduce from them the consequences relative to the diagnosis of diseases and the practice of medicine. This was an immense task, which did not, however, check the patient zeal of Bonet, his "*Sepulchretum*" being the outcome of his exertions.

In 1745, John Astruc (1684-1766), a native of Sauves, a town of Lower Languedoc, France, published his "*Tractatus Pathologicus*," a work which, although favorably received and eminently popular at the



Ioannes Baptista Morgagni

Interfectus Tertiis Aprilis MDCCXXVII

FIG. 3—GIOVANNI BATTISTA MORCAGNI (1682-1771)
An Italian anatomist, the founder of pathological anatomy

time of its appearance, has now become obsolete. In 1759, his two-volume work on tumors and ulcers¹⁵ was issued.

In 1765, Albrecht von Haller, the famous physiologist, two years after his return to his native town of Berne, in Switzerland, and amid the multitude of his public duties, found time to publish a valuable work on morbid anatomy.¹⁶

Pathological anatomy, however, as a distinct branch of medical study, originated with Giovanni Battista Morgagni (1682-1771), a very able and eminent anatomist, born at Forli, a small town in Italy. He first studied in his native place, but afterwards went to Bologna. He early displayed extraordinary talent, and in 1698, at the age of sixteen, began as a student of philosophy and medicine at Bologna, graduating with both faculties as Doctor three years later. He next became prosector to Valsalva, who had been a pupil of Malpighi, and succeeded him soon afterward as demonstrator of anatomy at the university. He subsequently became a professor at Padua (1715-1771), where he was appointed to the chair of theoretic medicine, which position he held with the highest honor till his death nearly sixty years later. It was not until his seventy-ninth year, after he had published several works, that he allowed his famous work on pathological anatomy to appear. This is the historical classic, "*De Sedibus et Causis Morborum per Anatomem Indagatis*"—"The Seats and Causes of Disease Revealed by Dissection." It consists of five books of letters, seventy in number, which were published by a systematic treatise, in two folio volumes, in Venice, in 1761. The work embraced the record of six hundred and forty dissections,* and gives a description of the morbid conditions of the body through its entire extent.¹⁷ Here, for the first time, the real object and aim of modern pathological anatomy is made manifest—namely, the bringing of postmortem findings into correlation with clinical records. Morgagni was a very versatile man, well informed in all branches of science and literature, and possessing a remarkable memory. His eulogist describes him as displaying the highest personal qualities of the physician: "*In observando attentus, in prædicendo cautus, in curando felix*"—careful in observing, cautious in predicting, fortunate in curing. With regard to his original observations in pathology, and to indicate, in a degree, the vast scope of his work, I cannot do better than quote the subjoined excellent summary as given by Garrison:¹⁸

"Morgagni gave the first description of cerebral gummata and disease of the mitral valve; early accounts of syphilitic aneurysm, acute yellow atrophy of the liver and tuberculosis of the kidney, and the first recorded case of heart-block (Stokes-Adams disease);¹⁹ identified the clinical features of pneumonia with solidification of the lungs, em-

* It is interesting to compare the 640 dissections made by Morgagni, with the 30,000 autopsies performed a century later by Carl Rokitsansky, M.D. (1804-1878), curator of the Imperial Pathological Museum and professor at the University of Vienna. This immense fund of materials formed the basis of Rokitsansky's grand work, entitled "*Handbuch der pathologischen Anatomie*," published in Vienna in three large volumes, during the years 1841-1846.

phasized the extreme importance of visceral syphilis, and was the first to show that intracranial suppuration is really a sequel of discharge from the ear, a phenomenon which even Valsalva had conceived the other way round. Morgagni also described what is known as 'Morgagnian cataract,' and he proved, in many autopsies, the Valsalva dictum that the cerebral lesion in apoplexy is on the opposite side from the resulting paralysis.²⁰ The 'De Sedibus' abolished humoral concepts in pathology for a long period of time."

Morgagni's legitimate successor was Matthew Baillie (1761-1823), a son of John Hunter's sister. Baillie, like Smellie, Cullen, and the two Hunters, was a native of Lanarkshire, Scotland. In 1793, in London, Baillie published his "Morbid Anatomy," the first treatise of its kind in the English language.²¹

Among other physicians of the eighteenth century, who occupied themselves with anatomicopathological researches, thereby adding new observations to those already known, particular mention should be made of G. D. Santorini,²² whose collection of "Observationes Anatomicæ" was published in Venice in 1724; of Edward Sandifort,²³ whose "Tabulæ Intestini Duodeni" was issued at Leyden in 1780; of Joseph Lieutaud (1703-1780), who wrote many valuable memoirs on botany, anatomy, the spleen, urinary bladder, heart and pericardium, and a Latin work upon the seats and causes of diseases which he had observed by the inspection of dead bodies; and, above all, to Marie-François-Xavier Bichat (1771-1802), termed the "Napoleon of Medicine," who gave utterance to the aphorism: "Take away some fevers and nervous troubles, and all else falls to the kingdom of pathological anatomy." Although Bichat's work was largely done in the closing years of the eighteenth century, he published but little ere the dawn of the nineteenth; hence, he more properly belongs to that period. Bichat once remarked, and his words are as full of meaning to-day as when first spoken:

"You may observe disease of the heart, lungs, abdominal viscera, etc., night and morning by the sick-bed for twenty years, yet the whole furnishes merely a jumble of phenomena which unite in nothing complete; but if you open a few bodies, you will see the obscurity speedily give way—a result never accomplished by observation if we do not know the seat of the disease."

Reckoning with the eighteenth century alone, bacteriology was virtually non-existent as a distinct branch of medical science. Not until the nineteenth century when, under the magic influence of such expert investigators as Koch, Pasteur, Davaine, Klebs, Welch, Gaffky, Löffler, Pfeiffer, Kitasato and their numerous pupils, the germ theory of disease became paramount, did bacteriology assume the rôle of a definite branch of medical study. Prior to this time, however, there were a few beacon lights along the route—straws showing, as it were, which way the wind was blowing. For example, as early as the middle of the seventeenth

century Athanasius Kircher (1602-1680) and Robert Hooke (1636-1703) employed the microscope in their efforts to determine the causes of disease; and Nehemiah Grew (1641-1712) had completed his studies in vegetable histology and physiology, publishing the results of his observations in 1671 and 1672. Later in the century Antony van Leeuwenhoek (1632-1723) was the first to see protozoa under the microscope (1675), and this same observer found microorganisms in the teeth in 1683.

The doctrine of a "contagium animatum" as the cause of infectious disease was a subject of much speculation, engrossing the attention of the early microscopists. Such a theory, however, first assumed definite shape and form in the writings of Girolamo Fracastoro (1484-1553), who, in 1546, published his treatise entitled "De Contagione," in which he states, with remarkable clearness, the modern theory of infection by microorganisms.²⁴ But Fracastoro nowhere refers to the latter as living organisms, thereby making the decision of priority in regard to the germ theory of disease a mooted question between himself and Athanasius Kircher.

In the works of Carl von Linné (1707-1778), or Linnæus, the great Swedish botanist who himself was a physician, the idea is expressed with more or less directness that the propagation of infectious diseases depends upon the implantation of minute independent organisms into or upon the affected individual. Linnæus also was awake to the possibility of malarial fever being water-borne. But it remained for the Italian clinician, Giovanni Maria Lancisi (1655-1720), in his great treatise²⁵ on swamp fevers, published in 1717, although professedly stating the doctrine of miasms, to first suggest the possibility of transmission by mosquitoes.

V. MATERIA MEDICA AND THERAPEUTICS

The status of materia medica and therapeutics in the eighteenth century, compared with that of the centuries preceding it, showed a decided advancement. The tendency toward the employment of simple remedies, in lieu of the "shotgun prescriptions" and loathsome mixtures formerly in vogue, was one of the distinctly favorable signs of the times. For generations blood-letting and cathartics were almost the only known remedies, in certain sections of the globe. Therapeutic fads likewise were losing their hold upon a gullible public, being superseded by vegetable and mineral preparations of known remedial virtue. Even the learned Dr. Johnson himself refers to one Joshua Ward, a famous quack ranking with the Chevalier Taylor, who made his fortune by the sale of antimonial pills and drops, and other nostrums. Famous female impostors of the period were Mrs. Mapp, a bonesetter, and Joanna Stevens, a widow, who, in 1739, actually succeeded in having her alleged remedy for stone in the bladder purchased by Act of Parliament. The recipe, published in the *London Gazette* of June 19, 1739,



William Cullen

FIG 4—WILLIAM CULLEN (1712-1790)

A highly-esteemed Scottish physician, chemist and clinical teacher of the eighteenth century

proved to be a most gruesome but probably harmless mixture of eggshells, garden-snails, swines' cresses, soap, and such vegetable ingredients as burdock seeds, hips, and haws.

Among the popular remedies of the time were quassia-cups, saffron drops, purging sugar-plums, and anodyne necklaces for pregnant women and teething children. "Tuscora rice," for consumption, the first American patent medicine, was introduced in 1711. The metallic or magnetic tractors of Elisha Perkins of Connecticut, patented in 1798, had a remarkable vogue at the time, effecting "cures" by stroking, their principle of action being analogous to that of galvanism or animal magnetism.

William Cullen, of the Glasgow and Edinburgh schools, laid great stress upon the agency of the *vis medicatrix naturæ*, a line of action adhered to by the leading physicians of the present day, with decided advantage. Bishop George Berkeley (1685-1753), an English clergyman and philosopher, author of "Verses on the Prospect of Planting Arts and Learning in America," in which poem occurs the following beautiful and well-known stanza:

"Westward the course* of empire takes its way;
The first four acts already past,
A fifth shall close the drama with the day;
Time's noblest offspring is the last;"

discoursed long and eloquently on the virtues of tar-water (1720-1748), exalting it to a position which was essentially that of a panacea for all human ills. But all the while the tendency was gradually toward that of a system of rational therapeutics, one in which drugs of known efficacy were to be employed, whose pharmacological action and toxicological effects, if they possessed any of the latter, had been proven by animal experimentation.

In 1736, John Tennent, of Virginia, published a first account of senega, or the Seneca snake-root, commending it most highly in the treatment of pleurisy, pneumonia, and the bite of the rattlesnake. William Heberden (1710-1801), of London, did a most important service to therapeutics when, in 1745, he published his celebrated "Essay on Mithridatium and Theriaca." John Huxham (1692-1768), of Devon, one of Boerhaave's pupils who had studied Hippocrates in the original, devised the familiar tincture of cinchona bark with which his name is associated; John Fothergill (1712-1780), a Quaker pupil of Alexander Monro *primus*, established his magnificent botanic garden, introducing kino and catechu into the London Pharmacopœia; and Anton Stoerck (1731-1803), of Swabia, the great champion of emetics, did a vast amount of very credible work in pharmacology and toxicology, the scope of his investigations including such familiar vegetable drugs as conium or hemlock (1760-1761), stramonium, hyoscyamus, and aconite (1762), colchicum (1763), and pulsatilla (1771).

The name of William Withering (1741-1799), of Shropshire, Eng-

* Often quoted "star of empire."

land, one of the ablest clinicians of his time, is ever memorable as the pioneer in the correct use of digitalis in affections of the heart. Withering, in 1776, having learned from an old grandame in Shropshire that fox-glove or digitalis was beneficial in dropsy, immediately set about trying it in heart diseases. He recommended its use wherever he could, and by 1783 he had the satisfaction of seeing it introduced into the *Edinburgh Pharmacopœia*. His "Account of the Fox-glove," a pharmacological classic, was published in 1785.

Dover's powder, the *Pulvis Ipecacuanhæ compositus*, was introduced into medicine by the famous buccaneer physician, Captain Thomas Dover (1660-1742), who was probably a house pupil of the great Sydenham, and, in 1709, rescued Alexander Selkirk (the original Robinson Crusoe) from the island of Juan Fernandes. Dover's formula for his "diaphoretic powder" is given in his "Ancient Physician's Legacy to his Country," published in London in 1732,^{26, 27} the sixth edition appearing ten years later.* In 1748, John Astruc²⁸ published his "Tractatus Therapeuticus"; John Leigh,²⁹ of Virginia, gained the Harveian prize in 1785, by his essay, "An Experimental Inquiry into the Properties of Opium," published in Edinburgh in 1786; and Johann David Schoepf (1752-1800), the old Anspach-Bayreuth surgeon, traveler and naturalist, who came out to America with the Hessian troops in 1777, remaining over after the war, published in 1787, at Erlangen, his scholarly "Materia Medica Americana," a pioneer work on the subject.³⁰

The first pharmacopœia to be printed in America was prepared by Dr. William Brown, of Virginia, who succeeded Benjamin Rush as Physician-General of the Middle Department. It consists of a pamphlet of 32 pages, designed for use in the Continental Army, and was issued anonymously from the military hospital at Lititz, Pennsylvania, in 1778. During the eighteenth century three new editions of the London "Pharmacopœia" were issued—the fourth, fifth and sixth, each characterized by changes showing the status of therapeutics and the gradual advance of pharmacology.³¹ The fourth "Pharmacopœia," edited by Sir Hans Sloane (1660-1753), a famous British physician and naturalist and virtually the founder of the British Museum, London, was issued in 1721, excludes many of the old syrups and waters, and introduces stramonium, gamboge, *Secale cornutum* or ergot, hepar, ipecac, tartar emetic, lunar caustic, lime-water, Ethiops mineral, spirit of sal volatile, iron sulphate, tincture of perchlorid of iron, and other inorganic preparations. The fifth London "Pharmacopœia," revised by Mead, Heberden, Freind, and others, and issued in 1746, contains many new tinctures, including those of valerian and cardamoms. Glauber's salts, sweet spirits of niter, syrup of squills, liquor potassæ, and potassium acetate were added. In the sixth "Pharmacopœia," appearing in 1788, practically all the animal materia medica has disappeared, while a large number

* The reader is respectfully referred to Professor (now Sir) William Osler's article, entitled "Thomas Dover, Physician, and Buccaneer," appearing in the *Bull. Johns Hopkins Hosp.*, lviii, January, 1896, and reprinted in his excellent and inspiring volume, "An Alabama Student, and Other Biographical Essays," pp. 19-36.

of new drugs and compounds are added. These include such familiar and useful preparations as aconite, arnica, castor oil, colomba, cascarilla, kino, quassia, magnesia, senega, ether, oxid of zinc, Dover's powder, Hoffman's anodyne, Huxham's tincture, James' powder, spiritus Mindereri, sarsaparilla decoctions, compound tincture of benzoin, extract of chamomile, tincture of opium, and "tinctura opii camphorata" (paregoric).

Allusion should be made to a famous toxicological case occurring late in the eighteenth century, in which the celebrated John Hunter was sworn in as an expert witness. It is that of the trial of Captain John Donellan,³² for the alleged willful murder, by poison (laurel-water), of his brother-in-law, Sir Theodosius Boughton. The trial was held at the Warwick assizes, in March, 1781, and Hunter was much perplexed upon finding himself unable to answer the simple, important questions put to him by Mr. Justice Buller, who presided. Impressed by this and other shortcomings of medical evidence in criminal trials, Andrew Duncan, Sr., through his repeated efforts, succeeded in having the Crown institute a chair of forensic medicine in the University of Edinburgh, the first in Great Britain, in 1806.

VI. THE PRACTICE OF MEDICINE

The practice of medicine, including general diseases, the major and minor exanthemata, and the special infections, presented a well-tilled field in the eighteenth century. At its very dawn, in 1702, Richard Mead (1673-1754), one of the five famous London physicians—Radcliffe, Mead, Askew, Pitcairn and Baillie—who successively carried the "Gold-headed Cane,"* published his earliest treatise, "A Mechanical Account of Poisons," which remains one of the classics in medical literature.³³ Mead's "Discourse Concerning Pestilential Contagion,"³⁴ and his essay "On Plague,"³⁵ could be consulted with profit by the medical student of to-day. Mead was the first to advocate quarantine to prevent the spread of plague, scarlet fever and kindred diseases.

In 1707, Georg Ernst Stahl (1660-1734), of Ansbach, Bavaria, published his "Theoria Medica Vera"—the "True Theory of Medicine."³⁶ Stahl and his followers were largely in favor of *placebos*, strenuously opposing the use of active drugs. Friedrich Hoffmann (1660-1742), a friend and fellow-student of Stahl, was a professor at Halle for nearly fifty years. He left an original description of chlorosis (1730), and was one of the first to describe rubella (1740). His work upon "Systematic Rational Medicine," written in Latin, was translated and passed through several editions.³⁷

The leading physician of the age was Herman Boerhaave (1668-

* "The Gold-headed Cane," edited by William Macmichael and first published in London in 1827. A second edition appeared in the following year. In 1884 a new edition, with interesting notes, was published by William Munk. In 1915 a new edition was published in New York, with an Introduction by Sir William Osler and a Preface by Francis R. Packard.



FIG 5—HERMAN BOERHAAVE (1668-1738)
famous Dutch physician, professor of botany, medicine and chemistry at
Leyden 1701-1729

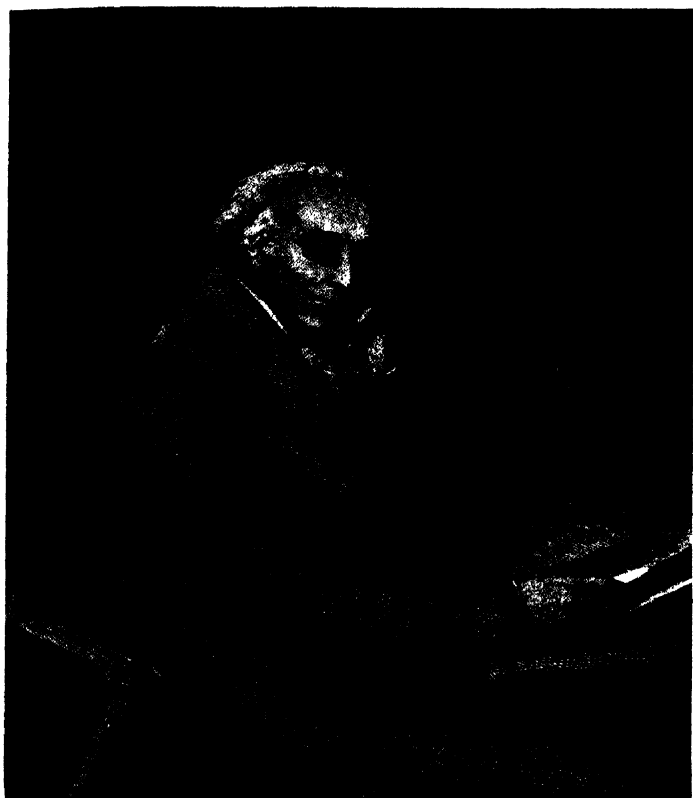
1738), the founder of the "Eclectic School." Boerhaave, sometimes called the "Modern Galen," is especially remarkable through his pupils, the list including Haller, Gaub, Cullen, Pringle, van Swieten and de Haen. His "*Elementa Chemicæ*," published at Leyden in 1732, was easily the best book on the subject throughout the eighteenth century.³⁸ As a clinician, he was the first to describe rupture of the esophagus, and the aura-like pain which precedes hydrophobia. He is also credited with being the first to establish the site of pleurisy exclusively in the pleura, and to prove that small-pox is spread only by contagion. In his clinics he was accustomed to using the Fahrenheit thermometer, a practice perpetuated by his pupils, van Swieten and de Haen.

One of the salient features of clinical medicine in the eighteenth century was the introduction of new methods of precision in diagnosis. A notable advance was made when Leopold Auenbrugger (1722-1809), a Styrian by birth, brought out his discovery of immediate percussion of the chest. His little book, the "*Inventum Novum*," published in the year 1761, though consisting of but twenty-two pages and unsalable in Auenbrugger's time, is to-day held worth far more than its weight in gold.³⁹

Another attempt to employ instruments of precision in diagnosis was recorded when, in 1707, Sir John Floyer (1649-1734), of Staffordshire, published his "*Physician's Pulse Watch*," which was the first effort for a hundred years to revive the studies of Galileo, Kepler, and Sanctorius in the matter of accurately timing the pulse.⁴⁰ Floyer tried to get the pulse-rate by timing its beats with a watch which ran for exactly one minute.

In the classic work of George Martine (1702-1741), of Scotland, published in 1740 and entitled "*Essays and Observations*," we find a revival of the subject of clinical thermometry.⁴¹ The clinical thermometer, another eighteenth century contribution to instrumental precision in medicine, had already been conceived and partly developed by Sanctorius, Boerhaave, de Haen, and Haller. Martine's ideas were carried into practice by James Currie (1756-1805), another Scotsman, in his "*Medical Reports*," published in 1798.⁴² Currie, who also has an enduring claim on our gratitude as the editor and biographer of Robert Burns, is remembered for having used cold baths in typhoid fever long before Brand of Stettin, checking up his results with the clinical thermometer.

William Cullen (1712-1790), one of the brightest names in Scotch medicine of the eighteenth century, was a native of Hamilton, in Lanarkshire, and began his career as a pupil of Monro *primus* in Glasgow. In 1740 Cullen took the degree of Doctor of Medicine from the University of Glasgow. Six years later he taught chemistry in Glasgow, and in ten years more came to Edinburgh as Professor of Medicine. He was the first medical lecturer to use the vernacular, instead of Latin (1757); and he was one of the first to give clinical or infirmary lectures in Great Britain. His "*Synopsis Nosologiæ Methodicæ*," published in 1769, was later opposed by Benjamin Rush, his most famous American



Benjamin Rush

FIG. 6.—BENJAMIN RUSH (1745-1813)

The greatest American physician of the eighteenth century

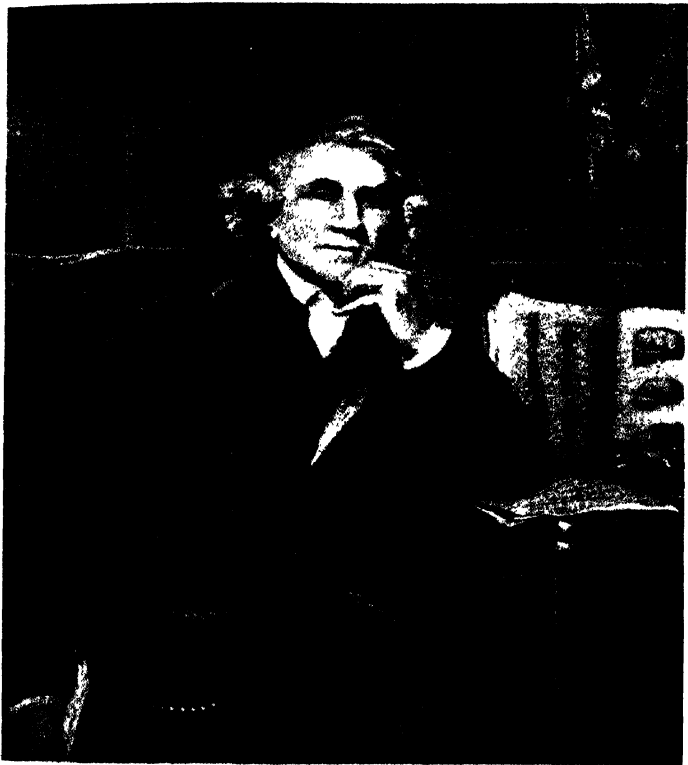
pupil.⁴³ His "First Lines of the Practice of Physic" (1776-1784) was for years an authoritative textbook in Great Britain and America.

William Heberden was a typical practitioner of the period, whose lifetime covered nearly the whole century. He was a Cambridge graduate of superior attainments; and his "Commentaries," written in Latin and published in 1802, contain his original descriptions of varicella (1767),⁴⁵ of angina pectoris—which was long known as "Heberden's asthma" (1768),⁴⁶ and of the nodules in the fingers ("Heberden's nodes") which occur in arthritis deformans (1802).⁴⁷

In 1775 John Huxham published his "Essay on Fevers," in which he gave careful and original observations of many infectious diseases, differentiating, in particular, between the "putrid malignant" and the "slow nervous" fevers—that is, between typhus and typhoid. As early as 1747 he recommended a vegetable diet in scurvy; and in his essay on malignant sore throat (1757), he was the first to observe the paralysis of the soft palate which attends diphtheria.

John Brown (1735-1788), of Scotland, sometimes styled the last systematizer of medicine, was a tutor in the family of William Cullen, and on some occasions assisted him in lecturing. Turning against his quiet teacher, he afterward undertook an independent course of lectures, promulgating doctrines of his own in opposition to those of his former patron. His theory, known as the "Brunonian system,"⁴⁸ in which diseases were classed as *sthenic* or *asthenic*, according as the vital condition or "excitement" is increased or diminished, attracted many followers, actually holding the attention of Europe for a quarter-century.

Gerhard van Swieten (1700-1772) did much to advance Austrian medicine, and created the world-famed Vienna clinic after the Leyden pattern. In America, Benjamin Rush (1745-1813), of Philadelphia, was the most conspicuous medical character of the eighteenth century. He was one of William Shippen's earliest students in anatomy, studied widely abroad, was a member of the Continental Congress, and one of the signers of the Declaration of Independence. On April 11, 1777, he was appointed surgeon-general of the Middle Department of the Continental Army. One invaluable result of his military experience remains in his pamphlet entitled "Direction for Preserving the Health of Soldiers." He described cholera infantum in 1773; dengue, in 1780;⁴⁹ and he was perhaps the first to note the disease which we now term thermal fever, describing it with great accuracy in "An Account of the Disease Occasioned by Drinking Cold Water in Warm Weather." His printed works were published in seven volumes, running through a number of editions. He also edited editions of some of the most famous English works, including those of Sydenham. Rush Medical College, Chicago, is named for him; and in 1904 a monument was erected to his memory, in Washington, D. C.



JOHN HUNTER

John Hunter

FIG. 7.—JOHN HUNTER (1728-1793)
A noted British surgeon, anatomist, and physiologist

VII. SURGERY, GENERAL AND OPERATIVE

The history of surgery will be touched upon but briefly, and only in its bearing upon practical medicine. One of the earliest surgical works of importance, published in the eighteenth century, was the "*Chirurgie*" of Laurence Heister (1683-1758), issued at Nuremberg in 1718.⁵⁰ August Gottlieb Richter (1742-1812) wrote a treatise on hernia (1777-1779),⁵⁰ which is still an acknowledged classic. In 1723, William Cheselden published his "*Treatise on a High Operation for Stone*."⁵¹ Charles White (1728-1813), of Manchester, first excised the head of the humerus in 1768, gave the first account of "white swelling" in 1784, and introduced the method of reducing dislocations of the shoulder by means of the heel in the axilla. Percival Pott (1714-1788), one of the best-known London surgeons, became especially eminent through his studies upon hernia, spinal disease, and diseases of the bones and joints. His complete *chirurgical* works appeared in London in 1771. He is eponymically remembered by the fracture of the fibula, with displacement of the tibia, which bears his name ("Pott's fracture"); and by vertebral disease or "caries" of the spine ("Pott's disease," "Pott's boss," or "Pott's curvature").

The eighteenth century produced John Hunter (1728-1793), one of the world's greatest surgeons. He was a younger brother of William Hunter, enjoying even a greater reputation than the latter. He was a pupil not only of his brother, but also of Cheselden and Pott. Beginning the practice of surgery in 1763, he became surgeon to St. George's Hospital in 1768, and Surgeon-General of the English forces in 1789. He is regarded as the founder of scientific surgery, being so memorialized on his tomb in Westminster Abbey. His studies of tendons laid the foundation for the operation for the cure of club feet. He discovered the "collateral circulation of the blood"—one of the most important discoveries in surgery. This led to his invention of the "Hunterian" operation for aneurysm, which has made the name of Hunter immortal in the annals of surgery. To the medical student his name is especially familiar, in connection with "Hunter's canal," the aponeurotic space in the middle third of the thigh; and by his differentiation between hard (Hunterian) chancre and the chancreoid ulcer. His four masterpieces are the "*Natural History of the Human Teeth*" (1771);⁵² the treatise "*On Venereal Disease*" (1786);⁵³ the "*Observations on Certain Parts of the Animal Economy*" (1786);⁵⁴ and the "*Treatise on the Blood, Inflammation and Gun-shot Wounds*" (1794).⁵⁵ the latter being a posthumous production upon which he had been long engaged.

John Abernethy (1764-1831), a devoted pupil of John Hunter, was regarded as his immediate successor in London. Abernethy was the first to ligate the external iliac artery for aneurysm (1796); and he also ligated the common carotid for hemorrhage, in 1798. He published several volumes of "*Physiological Lectures and Discourses*," and was

sterian orator in 1819. He believed that local diseases are either of constitutional origin,⁵⁶ or due to digestive disturbances.

With regard to the achievements of American surgeons in the eighteenth century, brief mention should be made of the courses of lectures in Anatomy and Surgery, delivered in 1763 and 1764, to a small class in Philadelphia, by William Shippen, Jr., a pupil of the Hunters. In 1761 an amputation of the shoulder-joint was performed by John Warren of Boston; and Wright Post, appointed professor of surgery in the Medical College of New York in 1792, performed the operation for a thoracic aneurysm by the Hunterian method in 1796.⁵⁷

VIII. GYNECOLOGY AND OBSTETRICS

The history of gynecology and obstetrics in the eighteenth century, brief though it is, will be jointly considered. It was not until late in the eighteenth century that an impetus was given to obstetric medicine. Until that time the conduct of this department was chiefly allotted to women, the few male practitioners entering therein being usually men of a lower grade of professional attainments. To William Hunter we are indebted for the new order of things. It was Hunter who established the dignity of obstetrics, elevating it to the position of a science, and opening the way to its rapid progress.

During the eighteenth century gynecology, as an independent specialty, had no real existence. A few papers, however, were published on the subject, and a small number of operations performed. Among these should be mentioned Robert Houstoun's treatment of an ovarian dropsy by tapping the cyst, in 1701; William Hunter's proposal of excision for ovarian cyst in 1757, and his description of retroversion of the uterus in 1770; three cases of laparotomy for extra-uterine pregnancy by John Bard, of New Jersey, in 1759, and by William Baynham, of Virginia, in 1791 and 1799; Sigault's symphysiotomy, in 1777; and Matthew Baillie's description of dermoid cysts of the ovary, in 1789. John Astruc published a six-volume treatise on diseases of women, in 1761-1765.

William Smellie (1697-1763) learned his obstetrics in Paris, settling in London in 1739. To him William Hunter came as resident pupil in 1741. Obstetrics owes much to the genius of Smellie. He introduced the steel-lock forceps in 1744, and the curved and double-curved forceps (1751-1753). His "Midwifery," issued in 1752, was the first textbook promulgating correct rules for the use of the forceps, and also giving explicit directions for differentiating contracted pelves from normal ones, by actual measurement.⁵⁸

William Hunter, Smellie's pupil, discovered the "decidua reflexa" and the separate maternal and fetal circulation, thus laying the foundation of modern knowledge of placental anatomy. His brother John also participated in this discovery. Unlike Smellie, William Hunter was opposed to the use of forceps. In 1778 he wrote a paper entitled,

"Reflections on Dividing the Symphysis of the Ossa Pubis"; and five years later (1783) his paper on infanticide appeared, entitled, "On the Uncertainty of the Signs of Murder in the case of Bastard Children."

The mechanism of labor was first considered by Hendrik Van Deventer (1651-1724), a native of Holland, in his "*Novum Lumen*," printed in 1701;⁵⁹ by Sir Fielding Ould (1710-1789), of Dublin, in his "*Treatise on Midwifery*," published in 1742;⁶⁰ and later by Smellie, André Levret, Peter Camper, and others. The obstetric treatise of Charles White, the Manchester surgeon, regarded as a pioneer work in aseptic midwifery, was published in London in 1733. Jean Palfyn (1649-1730), in 1720, reinvented or reintroduced the obstetric forceps; La Motte, in 1721, extended the use of podalic version to head presentations; and Jean Louis Baudelocque, Sr. (1746-1810), invented a pelvimeter in 1781.

The first public teacher of obstetrics in America was William Shippen, Jr. (1736-1808), who lectured on the subject in Philadelphia in 1762, thereby greatly advancing the cause of male midwifery.

IX. HYGIENE AND PREVENTIVE MEDICINE

The earliest works on hygiene relate to gymnastic exercises, to the location of cities and towns and the maintenance of cleanliness therein, to the construction of aqueducts, fountains, and sewers, to the sequestration of lepers, and the establishment of free baths for the poor. When syphilis took the place of leprosy, a part of the ordinances relative to leprosy were applied to syphilitics. The prevalence of plague in the East caused lazarettos to be established, and wise and strict regulations were promulgated, to preserve the people from the ravages of this disease. John Howard, in the eighteenth century, offered to the world the first example of a man who traveled solely for the love of humanity. Hospitals, prisons, and lazarettos attracted his attention; he devoted his fortune and his existence to the amelioration of the condition of the unfortunates who were shut up in them. The health of soldiers and seamen attracted the attention of many observers, giving rise to numerous noteworthy publications.

The publication, in 1700, of a work by Bernardino Ramazzini (1663-1714), entitled "*De Morbis Artificum Diatriba*," opened up an entirely new department of modern medicine—namely, the diseases and hygiene of occupations.⁶¹ "*The Divine Order*" of Johann Peter Süssmilch (1707-1777), the old Prussian army chaplain, published in 1742,⁶² is an epoch-making work in the development of vital and medical statistics, bringing together many data of capital importance in public hygiene, life insurance, and national polity. The great four-volume work of Johann Peter Frank (1745-1821), his "*Complete System of Medical Polity*," published at Mannheim in 1777-1788, constitutes the very foundation of modern public hygiene.⁶³

Sir John Pringle (1707-1782), a Scotch pupil of Boerhaave and



Edw. Jenner

FIG. 8.—EDWARD JENNER (1749-1823)

An English physician, celebrated as the discoverer of vaccination

Albinus, was the founder of modern military medicine and the originator of the Red Cross idea. In his "Observations on the Diseases of the Army" (London, 1752) he lays down the true principles of military sanitation, especially in regard to the ventilation of hospital wards." James Lind (1716-1794), a native of Scotland, the "father of nautical medicine," was the founder of naval hygiene in England. His fame rests upon three epoch-making treatises, those on scurvy (1754),⁶⁵ the hygiene of sailors (1757),⁶⁶ and tropical medicine (1768).⁶⁷ In this connection mention should be made of van Swieten's monograph on "Camp Diseases," published in 1758, at Vienna.⁶⁸ Sir Gilbert Blane (1749-1834), in his "Observations on the Diseases of Seamen" (1785),⁶⁹ recommended the use of lime-juice to prevent scurvy.

But of all the conquests which public hygiene has made in these latter times, there is one which merits a special mention—that of preventive inoculation. For centuries small-pox had prevailed, periodically, in both worlds; it took from the population of Europe an annual tribute which is estimated to have amounted to not less than four hundred thousand souls, and mutilated and disfigured nearly as many more. Indeed, its prevalence was so general that it became a common saying: "From small-pox and love, but few remain free."

Edward Jenner (1749-1823), a physician of Berkeley, a city of the county of Gloucester, having heard it said that the disease known in the western provinces of England under the name of cow-pox was communicated to those who kept or milked cows habitually, and that this affection, which was very slight, protected completely those who had passed through it, from the variolous affection, meditated on this strange fact, verified it, and conceived the happy idea of inoculating children, directly, with the virus taken from the udder of the cow. At the end of three, four, or five days he saw pustules developed, at all the points of the skin which he had pricked, similar to those of cow-pox; then the pustules broke, the pus dried and formed a small crust, which in falling left a cicatrix. Besides, there was little or no fever, the children continuing to eat and play as usual without realizing any bad symptoms. Not one of these children was ever attacked by small-pox.

Jenner, after having repeated his experiments for a number of years, and being assured of the innocuous character of the virus, and its prophylactic virtue, convinced finally of the reality and grandeur of his discovery, decided to make it public, and consigned all the details of the subject to a volume⁷⁰ printed at London, in the year 1798. It is a thin quarto, with four colored plates, dedicated to Parry of Bath. This book was followed, during the years 1799-1806, by five successive pamphlets, recording his subsequent experiments and improvements in technique up to the stage of recommending ivory points as the best vectors in inoculation

X. THE DISEASES OF THE EYE AND EAR

In the eighteenth century ophthalmology—the science which treats of the eye in health and disease—already had assumed a conspicuous place among the specialties in medicine. A number of excellent contributions were made to the literature of the subject, many brilliant and humane operations were performed, and the auxiliary topic—that of optics—was an attractive field sought by many investigators. Unfortunately, at this period, medical charlatans of both sexes also plied their trade as oculists, in a few instances, with a success which seemed almost incredible.

As early as the year 1700 Ramazzini, in his book on the "Diseases of Artisans," called attention to the eye-troubles of gilders, printers, and other occupations.⁶¹ In 1703, Georg Ernst Stahl's original description⁷¹ of lacrimal fistula appeared. Herman Boerhaave, in 1708, was the first to give a special course of lectures on ophthalmology. An ophthalmic contribution of note was Sylvester O'Halloran's treatise on glaucoma in 1750.⁷²

In 1752 the surgery of the eye received an important uplift, at the hands of Jacques Daviel (1696-1762), the originator of the modern treatment of cataract by excision of the lens. Heberden, in 1767, described night-blindness or nyctalopia; and John Dalton, in 1794, contributed his account of color-blindness. Joseph Beer's innovation of tridectomy was promulgated in 1798; and Thomas Young (1773-1829), the "father of physiologic optics," in 1801, gave the first description of astigmatism, with measurements and optical constants.⁷³

Michael Barth, in 1773, under royal patronage, established the Vienna school of ophthalmology.

Otology also made marked progress in the eighteenth century. The structure and physiology of the ear were carefully studied, important investigations on these points being made by Valsalva (1717),⁷⁴ by Scarpa (1772-1789),⁷⁵ and by Cotugno (1774).⁷⁶ The morphological essays of Geoffroy (1778),⁷⁷ and of Comparetti (1789),⁷⁸ are contributions of the highest order. John Hunter's paper, entitled "Account of the Organ of Hearing in Fishes" (1782), is one of the most remarkable of the early contributions upon this subject.⁷⁹ Guyot, in 1724, made the first attempt at catheterization of the Eustachian tube, an otological feat subsequently performed by Archibald Cleland in 1741. A strolling jockey, Eli by name, is credited with the first perforation of the tympanic membrane for deafness (1760), Jonathan Wathen, five years previously (1755), having treated catarrhal deafness by means of injections into the Eustachian tube through a catheter inserted in the nose.

It is still more important to note that the mastoid process was opened for the first time in the history of surgery by Jean-Louis Petit (1674-1750), of Paris, the leading French surgeon of the eighteenth century. Petit performed the operation in 1736, and it is described in his posthumous surgical treatise.⁸⁰ Subsequently to Petit, the mastoid

operation was successfully performed by the Prussian army surgeon Jasser in 1776, by J. H. G. Fielitz, and A. F. Löffler, and by the Danish surgeon Alexander Kölpin in 1796.

The Abbé Charles-Michel de l'Épée (1712-1789) founded the first school for deaf-mutes in Paris, in 1755, maintaining it at his own expense. In America the earliest advocate of education of the deaf was Francis Green (1742-1809), of Boston, Massachusetts. Green published his treatise, "*Vox Oculis Subjecta*," in London, in 1783.⁸¹

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CHAPTER V

HISTORY OF MODERN MEDICINE*

(During the Nineteenth and Twentieth Centuries)

By MAX KAHN, M.A., PH.D., M.D.

The world was in the midst of upheaval at the beginning of the nineteenth century. The rat-a-tat of the military drums was heard all over Europe. The time was out of joint and hordes of men stood up in arms to struggle for liberty. It had taken centuries of oppression to make the yoke so heavy for the downtrodden, that they overthrew, with volcanic violence, thrones and principles, royalty and clergy—parasites that had thriven on the sweat and toil of the masses. The conflagration begun by the fall of the Bastille spread to other countries, and with the succeeding eruptions of 1831, 1848 and 1871, western Europe became more and more democratized, and an epoch of rationalism was established which resulted in glorious achievements not encountered in any other century of history.

The masses may mock God, but they always fear the Devil. It takes longer to eradicate superstition than to implant science. Men overthrow governments, demolish churches, declare that the Age of Reason prevails, but in the limited mind of the "great majority" there yet linger that fol-de-rol of the clergy and the fi-fu-fum of the quack, which are supposed to have such magical properties and which yield such golden returns to the coffers of that great army of charlatans.

It has always been the principle and practice of the "respectable" established religion or profession to oppress and persecute all men who would reason and question their theories, who feared not to speak the truth as they knew it, or who discovered newer facts which controverted their false doctrines. All so-called established opinions are alike in this. The old refuse to change. Witness the condemnation of Socrates by the Greeks, the martyrdom of Jesus by the Jews, the persecution of Galileo by the Catholic Church, the burning of Servetus by Calvin, and the oppression of Paré by the Parisian Faculty.

To speak of the history of medical practice previous to the nineteenth century is really to speak of the history of quackery, or rather of the history of men who in their hearts knew that they were thriving

*It is not proposed in the limited space allotted to this Chapter to discuss in detail "dates and battles" in the history of Medicine during the last one hundred and twenty years. An attempt will be made to describe currents in medical thought, and personal mention will be made of those men only who lit new torches to guide the way for those that follow, and who stand, rock-fast, against the eroding influence of time and human forgetfulness.

on the ignorance of the public. Mature consideration makes one justify Molière's description of a physician of his time:

"Longue peruque, habit grotesque,
Affecter un air pedantesque,
Cracher du grec et du latin,
Tout cela reuni fait presque
Ce qu'on appelle un médecin."

And when one reads the medical therapy advised by the physicians of that period, one assumes that the physician may have thought that his remedy will prove effectual due to the gruesomeness and incongruity of the concoction, or, perhaps, to the prayers that were advised to be chanted simultaneously. It is, perchance, the prayers that may have helped his patients; it is certain that his medicaments did not aid, if they did not harm, the sick.

After that great period of mental darkness which pervaded Europe, when the Church of Rome reigned supreme, there was inaugurated another epoch characterized by the historic fact that tyranny changed hands, and though the so-called strivings for religious liberty resulted in the establishment of newer churches, it meant only the foundation of new theories of fanaticism; for, while until the sixteenth century only Rome murdered thousands at the auto-da-fés and at St. Bartholomew's nights in the name of religion, the "liberty" attained after the sixteenth century was that in certain countries the Protestants gained the power to burn and hang heretics, Catholics and all other non-conforming Protestants. It was not that Justice or Enlightenment had triumphed. It was only that the power to do wrong was wrested from a certain group of hands and wielded by another.

The Church could not stop all progress. There was Bacon pleading for experimentation and urging that "To know truly is to know the cause"; there was the great school of anatomists who began to describe the body structure; there was Harvey, who noted the circulation of the blood. However, in the eighteenth century there prevailed the system of theorization and classification which infested the work of every great man of that time. Volumes were written to prove or disprove fantastical theories, not after due experimentation in a laboratory, but after ponderous thought in the library. There was the "phlogiston" school, the school of "vitalism," the iatro-mechanical and the iatro-chemical schools, the Brunonian theory, and others. Scientists of that day seemed not to desire to delve in the unknown, but to classify and ratiocinate on the things that were known, or rather were thought known.

But, towards the end of the eighteenth century, the old order of things began to shake and topple over, and scientific reform, like political reform, made great progress. - Great times produce great men, and we find in the beginning of the eighteenth century thinkers in Western Europe, who after speculations and investigations, laid the foundations of the newer science of the modern period.

Of the absurd theories current at the beginning of the nineteenth

century, the one of the vitalistic production of organic substances was the most pernicious. It was assumed that no organic chemical substance could be prepared in the laboratory; that only the living body can do it, and therefrom the learned professors drew the moral that some unknown "vital" force was present in the living organism which it was useless to investigate, and which alone is able to produce all organic compounds from those of simpler to those of higher composition.

In 1828, Friedrich Wöhler (1800-1882) demonstrated that such an essentially organic compound as Urea could be prepared by heating ammonium cyanate, a substance easily prepared from its constituent elements. This simple experiment revolutionized the conception of the chemistry of life processes, and inaugurated an era of organic chemical research which ultimately resulted in the synthesis of such highly complex compounds as the polypeptids and the carbohydrates by Emil Fischer. This discovery of Wöhler, and his other discovery of the synthesis of hippuric acid by the body after the ingestion of benzoic acid, was the beginning of the study of the chemistry of the life processes going on in the animal economy. To these body chemical changes Liebig gave the name of "Metabolism" (Stoffwechsel). (1842).

The two greatest names in biological science during the nineteenth century are those of Darwin and of Pasteur. To appreciate truly the great advances of Medicine requires but to know the lives of those two eminent men, both of them pure in thought, honest in their actions and truly saints in their relations with their fellowmen. There are no greater men than these two.

The great question of the origin of man was always considered settled by the theologian and ever pondered upon by the scientist. All species were created by the special design of a divinity, said the theologians, and the individual male and the female of the species were saved in the Ark, when it pleased Providence to destroy all the world's occupants. Thoughtful men doubted this church doctrine, but could come to no other conclusion. Robinson writes, "To Buffon belongs the high honor of first scientifically discussing the origin of species by development. But Buffon lived in the priest-pested age of Louis XV, when the Bastille cast its shadow on the brain of every thinker. And Buffon thought of the chains that eat out the flesh, and the dungeons which the sun cannot find, and then he ended his arguments thus: 'But to us, it is certain from revelation that every species was directly created by a separate fiat.'"

The Theory of Evolution, advanced by Darwin in 1859 in his great book "On the Origin of Species by Means of Natural Selection," was propounded so clearly, and the evidence arrayed so masterfully, that the scientific world was almost immediately converted. Only priest and minister dared raise the cry of Atheist against Darwin, but truth conquered these also. And great men such as Spencer and Huxley, and Haeckel and Weissmann arose in England and in Germany and spread the teachings of Darwin, so that the whole science of Biology was revolutionized. One of Darwin's disciples, Thomas Henry Huxley,

declared he was more solicitous for the principle of freedom of thought than for the mere advancement of science, and this is the great good that Darwin and his followers have accomplished, for with Huxley they believed that "there is no alleviation for the sufferings of mankind except veracity of thought and action and the resolute facing of the world as it is, when the garment of make-believe by which pious hands have hidden its uglier features is stripped off."

The influence of Darwin, Wallace and their disciples was mainly on Biology and, therefore, only indirectly on Medicine which is founded on the biological sciences. Their philosophic conceptions permeated all the then known branches of knowledge, and inspired men to reinvestigate older conceptions, and to seek new explanations for the causes of phenomena in Nature.

But while Darwin's influence on Medicine was indirect, the epoch-making investigations of Pasteur are of such fundamental importance that many of the very conceptions of modern medicine have their birth in his experimental discoveries. For his influence was far-reaching. He not only investigated the older sciences, but he established new schools of learning, and to him is due our basic facts in bacteriology, immunology, and serology, and our principles of asepsis and antisepsis upon which modern surgery is based, and our knowledge of vaccination in certain diseases.

The life of Pasteur* is full of inspiration to him who would make Science his religion. He was born in the small town of Dole, in 1822. His father, a veteran of the Napoleonic wars, was a tanner, who, though poor, insisted that his son receive a good education. Accordingly, after preliminary studies, Louis Pasteur arrived in Paris, and studied the Natural Sciences, particularizing in Physics and Chemistry. We shall follow his discoveries in chronological order:

His first great contribution was in 1848, when he was twenty-six years old. Of this discovery, Professor Cohen writes: "Pasteur did not range far into the field of chemistry, but during the few years that he labored at the subject he struck so rich a vein of scientific wealth that, after the lapse of half a century, it still remains unexhausted." The investigation in question concerns the Nature of the two isomeric compounds, tartaric and racemic (paratartaric) acids.

Pasteur found that on crystallization of the tartrates, the crystals formed, while similar in general appearance, had the facets differently situated in the different crystals, so that their resemblance and their distinction were analogous to the similarity and difference which exist between the right one and the left of a pair of gloves. The forms were *enantiomorphous*. Pasteur separated the crystals in the presence of Biot, the great French chemist, and demonstrated to him that one form of the crystal turned the ray of polarized light to the right, and the other form to the left, while the mixture of the two in equal quantities produced a solution which was inactive. Biot, who had doubted Pas-

* A very sympathetic life of Pasteur has been written by René Vallery-Radot in French, and has been translated into English by Mrs. R. L. Devonshire.

tear's ability before, embraced him at the successful completion of the demonstration, and said to him: "My dear boy, I have loved Science so much during my life, that this touches my very heart."

His next great work was on fermentation and spontaneous generation. Do living bodies arise from parent living bodies, or are they under certain circumstances generated spontaneously? Is it a fact, as one man wrote, that given an old boot with soiled rags and pieces of cheese in it, young mice will spontaneously develop there? Since the days of Aristotle the theory of spontaneous generation was generally accepted. It was thought that frogs and toads and other animals arose from the mud of the brooks and ponds due to the life-giving influence of the sun's rays. In the seventeenth century, Alexander Ross, commenting on Sir Thomas Brown's doubt as to whether mice may be bred by putrefaction, flays his antagonist in the following words:¹ "So may we doubt whether in cheese and timber, worms are generated, or if beetles and wasps in cow dung, or if butterflies, locusts, shell-fish, snails, eels and such life be procreated of putrefied matter, which is to receive the form of that creature to which it is by formative power disposed. To question this is to question reason, sense and experience. If he doubts this let him go to Egypt, and there he will find the fields swarming with mice begot of the mud of the Nylus, to the great calamity of the inhabitants!"

The work of Redi (1626-1697), an Italian scientist, confirmed by the experiments of Swammerdam (1637-1681) and of Vallisnieri (1661-1730), with putrefying meat served to prove that all visible life came from ova deposited by insects in matter allowed to putrefy. But with the study of microscopic life by Leeuwenhoek, the question assumed a new form. A certain English Jesuit, Needham (1713-1784), and his contemporary, Lazarus Spallanzani (1729-1799), then took up the question, the former seeming to demonstrate that there is such a thing as spontaneous generation and the latter absolutely denying it. Their experiments made on vegetable and meat extracts subjected to heat in glass vessels seemed to yield different results in the hands of Needham and of Spallanzani.

The question of spontaneous generation was seemingly settled by the experiments of Franz Schulze and of Theodore Schwann, whose work convinced the scientists of those days that there is no basis for belief in the spontaneous origin of life. But the whole question was reopened by the Frenchman, Pouchet, who made the following experiment: He filled a flask with water and sealed it with great care. This flask he inverted over a mercury bath, and opened the neck of the bottle while under the mercury. The water he partially drove out by passing into the flask oxygen generated from salts. He now introduced with a sterile forceps a few granules of hay heated in an oven to a high temperature. After a few days he found that the hay was swarming with microscopic life. "Where," exclaimed he, "does this life come from? It cannot come from the water, which had been boiled, destroying all living germs that may have existed in it. It cannot come

from the oxygen, which was produced at the temperature of incandescence. It cannot have been carried in the hay, which had been heated for a long period before being introduced into the water." According to him, therefore, this life was of spontaneous origin.

It was at this time that Pasteur took up the question, contrary to the advice of his friends. He proved that the mercury of Pouchet's experiment contained dust particles which infected the water. What he did not know was that hay contains many spores which it is very difficult to destroy by ordinary heat, and which vitiated the results of Pouchet's experiments.

Let us hear his lecture:

"Here," he said, "is an infusion of organic matter, as limpid as distilled water, and extremely alterable. It has been prepared to-day. To-morrow it will contain little animalculæ, little infusories, or flakes of moldiness.

"I placed a portion of that infusion into a flask with a long neck, like this one. Suppose I boil the liquid and leave it to cool. After a few days, moldiness or animalculæ will develop in the liquid. By boiling I destroy any germs contained in the liquid or against the glass; but that infusion being again in contact with air, it becomes altered, as all infusions do. Now suppose I repeat this experiment, but that before boiling the liquid I draw (by means of an enameler's lamp) the neck of the flask into a point, leaving, however, its extremity open. This being done, I boil the liquid in the flask, and leave it to cool. Now the liquid in this second flask will remain pure, not only two days, a month, a year, but three or four years—for the experiment I am telling you about is already four years old, and the liquid remains as limpid as distilled water. What difference is there, then, between those two vases? They contain the same liquid, they both contain air, both are open! Why does one decay and the other remain pure? The only difference between them is this: in the first case, the dust suspended in the air and their germs can fall into the neck of the flask and arrive into contact with the liquid, where they find appropriate food and develop; thence microscopic beings. In the second flask, on the contrary, it is impossible or, at least, extremely difficult, unless air is violently shaken, that dusts suspended in air should enter the vase; they fall on its curved neck. When air goes in and out of the vase through diffusion or variations of temperature the latter never being sudden, the air comes in slowly enough to drop the dusts and germs that it carries at the opening of the neck or in the first curves.

"This experiment is full of instruction; for this must be noted, that everything in air save its dusts can easily enter the vase and come into contact with the liquid. Imagine what you choose in the air—electricity, magnetism, ozone, unknown forces even, all can reach the infusion. Only one thing cannot enter easily, and that is dust, suspended in air. And the proof of this is that if I shake the vase violently two or three

... in a few days it contains animalculæ or moldiness. Why? Because air has come in violently enough to carry dust with it.

And, therefore, gentlemen, I could point to that liquid and say to you, I have taken my drop of water from the immensity of creation, and I have taken it full of the elements appropriated to the development of inferior beings. And I wait, I watch, I question it, begging it to recommence for me the beautiful spectacle of the first creation. But it is dumb, dumb since these experiments were begun several years ago; it is dumb, because I have kept it from the only thing man cannot produce, from the germs which float in the air, from Life, for Life is a germ and a germ is life. Never will the doctrine of spontaneous generation recover from the mortal blow of this simple experiment."

These experiments of Pasteur attracted the attention of the young English surgeon, Joseph Lister (1827-1912), and ultimately resulted in that wonderful application of these discoveries, one of the greatest boons to suffering mankind. The hospital conditions of those times were something fearful. Death stalked in gruesome shape in every ward where surgery was done. A serious surgical operation was in reality a death warrant. All surgical wounds were supposed to show "laudable pus." The pus was not "laudable" if the patient died, "laudable" if the patient recovered. Surgeons used to attire themselves in leather aprons and in old work-a-day suits, as a present time butcher or cobbler does, and would not wash their hands before an operation, for they were sure to get soiled during the operation. Certain surgeons had a mortality list of over eighty per cent. of their cases. Conscientious men, frequently disgusted with such results, gave up the practice of surgery.

Lister was highly impressed with this awful mortality list from septicæmia, pyæmia, erysipelas, tetanus and hospital gangrene. Although he followed the accepted technic of the time in his amputation cases, used silver wire sutures, had free drainage and frequently changed the dressing, the death rate among his patients was forty-five per cent. He began to doubt whether any pus was "laudable," and became convinced that surgical healing by first intention was the proper way. But how obtain this desirable consummation in his cases? He directed his attempts at preventing the animalculæ and germs that infest the air from reaching his patients' wounds in a viable state. Heat was impractical, but he could use chemical disinfectants, and finally he used (August 12, 1865) a carbolic acid solution in a case of compound fracture with complete success. In Lister's wards, all the instruments and dressings were first disinfected in a strong phenol solution, similar precautions being used for the hands of the surgeon and his assistants. In the operating room, a kettle was constantly boiling, vaporizing carbolic acid into the atmosphere. The wounds were dressed with a sort of gauze soaked in this solution. This was Lister's method, in brief. This revolutionized the entire practice of surgery, and deft physicians ventured to operate on the peritoneal viscera, on the blood-vessels, on the brain, with remarkable results.

Before Pasteur and before Lister, Oliver Wendell Holmes (1809-1894), in Boston, in 1843, and Ignaz Philip Semmelweis (1818-1865), a Hungarian, in 1847, observed that puerperal fever was induced in most cases by the uncleanness with which the physician attended to his cases. Instead of helping and healing, the obstetrician of those days infected and inflicted injury and sometimes mortal injury on his innocent patients. Semmelweis observed that with proper precautions and with extreme cleanliness, he could reduce his mortality rate in the obstetrical clinic from almost ten per cent. to as low as one per cent. His method consisted in washing his hands in a solution of chlorid of lime before attending or examining his patients.

Both Holmes and Semmelweis were bitterly attacked. The orthodox, conservative obstetricians of that time heaped so much abuse on Semmelweis that he left Vienna and went to Budapest, where his broodings led to insanity and to an early death. Of the great men who have done good in the world, this Hungarian physician must be counted as one. For he has helped all mothers the world over. In their hour of greatest pain and greatest need he has assured them of a safe confinement. When, in 1883, Lister heard of Semmelweis, he honestly declared that to him belonged the precedence of originating antiseptic surgery.

Pasteur's studies in fermentation of vinegar led him to the discovery that this process is produced by a rod-like organism, the *Mycoderma aceti*. This discovery was met, as usual, with great contention and dispute, but Pasteur, as always, was right. He then began to investigate certain problems which had rather an important economic side to them. The great industries of France are the manufacture of wine, silk and wool, and any deleterious influence on the proper production of these commercial products will react badly on the economic condition of the industrial classes.

The wine industry was troubled because so much of the manufactured wine was spoiled before being consumed by the public. This was due to the molding of the wine by microorganisms. It was also endangering the export wine trade, for the wine deteriorated during the long journeys to foreign countries. Pasteur investigated this problem and recommended that the wine be preserved by heating it at a temperature of 55° to 60° C. This partially sterilizes the wine and prevents its deterioration. To this process the name "pasteurization" is given. Its practical application in the conservation and preservation of all foodstuffs is known to all.

His discoveries of silk-worm disease and the method of its prevention won for him the gratitude of his fellowmen, for thereby he saved for France an industry which was fast becoming ruined. Some time later he found the vaccine against sheep anthrax, reducing the mortality among cattle from this disease to less than one per cent. His success with anti-anthrax inoculations led him to experiment with the treatment of hydrophobia by a similar method. In 1885, he described his success in the treatment of a boy who had been bitten by a rabid dog by means of injections of a vaccine obtained from the spinal

arrow of infected animals. This discovery led to the establishment of Pasteur Institutes for the administration of such inoculations in every big city in the world.

In 1878, he described the *Staphylococcus pyogenes aureus* in boils, which he called "microbes en amas de grains," and the *Streptococcus pyogenes* in puerperal septicemia, called by him "microbe en chapelet de grains." In 1880 he described the pneumococcus.

Pasteur's work was so inviting for further investigation, that brilliant men in all lands began to study this new science of Bacteriology. It had been advanced as a theory by Jacob Henle (1809-1885), a great Jewish physician, in 1840, that certain infectious diseases are due to a *contagium animatum*, and he emphasized the fact that fever is only a symptom and not a disease. This teaching of Henle profoundly influenced that earnest young German, Robert Koch (1843-1910), so that to vary the stupid monotony of general practice, he made private investigations in microscopic life. One of the largest bacteria known is the anthrax bacillus, discovered in 1865 by Casimir Davaine, and it was this organism that Koch first studied. In 1876, he had completely worked out the life cycle of the bacillus, and he reported it to Ferdinand Cohn, the great botanist of Breslau. Koch's results were completely confirmed by Pasteur. Discovery followed discovery, and Koch established the first technic of modern bacteriology. His fixing methods and his staining processes made it easy for any young student to study microbic life. He described six of the common organisms present in traumatic infections, developed the technic of plate cultures, discovered the tubercle bacillus, 1882, the cholera bacillus, 1883, and then developed his famous Postulates, the Decalogue of the bacteriologist. In 1906, he discovered in atoxyl the remedy for sleeping sickness, the pest of the African jungle.

We must mention several more bacteriologists, for it was they who made diagnosis in infectious diseases a science. Edwin Klebs (1834-1913), Friedrich Löffler of diphtheria fame, Albert Neisser, who discovered the gonococcus, Carl Joseph Eberth, who described the typhoid bacillus and others. Among famous American bacteriologists one should not fail to mention William Henry Welch, Simon Flexner, and Theobald Smith.

That great plague of man, the curse of Venus, syphilis, has been lately robbed of many of its terrors. Its cause was unknown until Fritz Schaudinn (1871-1906) described that highly motile, corkscrew-shaped spirochete which he named *Spirocheta* or *Treponema pallida*, and which was later cultured in pure form by Hideyo Noguchi. But the greatest boon in the treatment and diagnosis of this disease was discovered by Paul Ehrlich (1864-1916) and by August von Wassermann, two famous Jewish scientists.

Pasteur's and Koch's experiments led to the development of specific serotherapy in various diseases. In 1890, Emil von Behring described the serum method for the treatment of diphtheria, and it is now universally accepted as a specific for this disease. Excellent re-

sults were also obtained in the treatment of tetanus infection by anti-toxin.

The genius and experimentation of Ehrlich and of Metchnikoff have established the sciences of immunology and serology. In 1883, when Eli Metchnikoff (1845-1917) showed that certain of the body cells, and especially the polynuclear neutrophile leukocytes, were active in the defense of the human body against invasion by microorganisms, a great advance was made in the understanding of immunity. This theory of phagocytosis is an easily demonstrated fact. According to this law, certain of the body cells are able to ingest an infecting parasite, a red corpuscle or other cell in the same manner as an amoeba ingests a food particle, and to dispose of it by intracellular digestion through the agency of ferments known as "cytases."²

But the great concept of Immunity was advanced by Ehrlich in 1885. Twenty years previously, August Kekulé had revolutionized and widely broadened the horizon of Organic Chemistry by suggesting that the benzol ring, composed of six atoms each of carbon and hydrogen, be imagined to conform to a regular hexagon. This induced Ehrlich to assume a similar hypothesis for his theory of Immunity. According to this assumption, the protoplasm of the cell consists of a central group of molecules (*Leistungskern*), in which the inherent vital characteristics are located, and whose integrity are necessary for normal cell life. The numerous molecules are assumed to be supplied with numerous side arms, or side-chains, which are capable of uniting with various substances with which they may come in contact — foods, toxins, and other harmful bodies. In order that nutritive matter may be taken up by the cell it must possess a certain conformation which will enable it to unite, or dovetail in, with the conformation of the side-chain. This conformation may be imagined as the relationship of a key to the lock—they must fit; in the words of Ehrlich they must be homologous. Ehrlich called the side-chains "receptors," and the foreign group which unites with it "haptaphore."

Based upon this hypothesis, Wassermann developed a method for the diagnosis of syphilis by means of fixation of the complement, a phenomenon discovered by Jules Bordet and Octave Gengou of Brussels. This has markedly facilitated the diagnosis of luetic infection, and has given the physician an idea as to the course of the specific treatment of this disease. The great climax of Ehrlich's life was the discovery of salvarsan, that wonderful organic arsenical preparation which acts so markedly in the cure of syphilis.

The advance in the study of Immunology attracted attention to a phenomenon of toxic reaction to foreign protein. In 1798, Edward Jenner had observed that certain patients react very badly upon being inoculated with variola vaccine a second time. In 1839, François Magendie (1783-1855) proved that after initial parenteral administration of egg albumen, a subsequent injection of this substance in rabbits will cause death. This phenomenon was also noted, in 1894, by Flexner in dogs which had received a second injection of dog serum. To this

phenomenon, Richet, in 1903, gave the name "anaphylaxis." This was especially investigated by Theobald Smith, Arthus, Milton Rosenau, Anderson, Vaughn and others. Nowadays many ailments are ascribed to anaphylaxis, such as asthma, various food allergies, etc. This syndrome is accompanied by a sudden and severe fall in blood-pressure and temperature, leukopenia, and local and general eosinophilia, a phenomenon first pointed out by Eli Moscheowitz (1911). *

If the nineteenth century had done nothing else for humanity except introduce that great blessing to the suffering of the world, that supple-
menter of natural sleep, whereby the tortured, pain-racked patient may close his eyes in oblivion, and forget for some few sweet hours his agonies—if only that alone were discovered, it would rank great amongst the centuries of accomplishment. To this condition of voluntary, blissful sleep, the poet-physician, Holmes, gave the name "anesthesia." *

It is too bad that the American to whom the credit is due for the general introduction of ether anesthesia, in his attempt to keep a secret the nature of the anesthetic, and in his endeavor to patent an apparatus for its administration, should have given rise to a heated and undignified controversy on this subject. Several men claimed the honor of being the originators of this idea. Time, however, has definitely awarded to William T. G. Morton (1819-1868), of Massachusetts, the palm for being the first man to make etherization a general practice. In 1800, Sir Humphry Davy (1788-1829) had experimented with nitrous oxid, and had pointed out³ that "it may probably be used with advantage in surgical operations in which no great effusion of blood takes place." This fact was known to an American dentist, Horace Wells (1815-1848), who used this anesthetic gas (1844) in his practice, until an unfortunate accident causing the death of one of his patients discouraged him from this procedure. Wells had communicated his experiments to Morton, who, dissatisfied with the use of the gas, hunted for another agent. An acquaintance of his, Charles T. Jackson, informed him that sulphuric ether may be used as an anesthetic. It has now been established by Young⁴ that Crawford W. Long of Georgia had removed in 1842 a small cystic tumor on the neck of a patient under the influence of ether, but as Welch states "we cannot assign to him any influence upon the historical development of our knowledge of surgical anesthesia or any share in its introduction to the world at large."

John C. Warren of the Massachusetts General Hospital performed the first surgical operation under ether at the request of Morton. The following⁵ is an extract of the records of that hospital for October 16, 1846: "This case is remarkable in the annals of surgery. It was the first surgical operation performed under the influence of ether. Dr. Warren had been applied to by Dr. Morton, a dentist, with the request that he would try the inhalation of a fluid . . . effectual in preventing pain during operations on the teeth. Dr. Warren . . . satisfied . . . that

* The word "anesthesia" occurs first in Plato (Timæus), and is used by Dioscorides in the modern sense. (Wm. Osler, "Annals of medical history," 1917. Vol. I, p. 329.)

the breathing of the fluid would be harmless, agreed to employ it. . . .” The case was a “congenital, but superficial vascular tumor, just below the jaw, on the left side of the neck.” It is said that when the operation was over, and the patient awoke, Warren exclaimed, “Gentlemen, this is no humbug!”

Imagine a surgical operation in the pre-anesthetic days. The shrinking patient is brought in by several strapping fellows to hold him down. The surgeon, a strong-minded, bluff-mannered man, comes in, and is greeted by the attendants and the expectant students. The doctor looks around, nods to the students, speaks kindly and encouragingly to the fear-haunted patient, and proceeds. The operation is amputation of the lower limb for gangrene. The surgeon rolls up his sleeves, takes up the glistening, sharp amputation knife, exposes the site of operation, and rapidly cuts. . . . Imagine the terrible, horrifying shriek of the patient, who is subdued to impotence by the attendants. The surgeon works fast. Heads of perspiration are on his forehead. The limb is off in four minutes. . . . The patient has mercifully fainted. . . . Swathes of bandages are now used in wiping off the blood; the sutures are inserted and the limb bandaged. . . . A young student may have fainted, and his fellows are reviving him, mocking his faint-heartedness. . . . The surgeon wipes his hand on some rag, attends to his sleeves, which may have rolled down, and is ready for the next case.

A little after Morton's popularization of ether, James Young Simpson (1811-1870) of Scotland used chloroform anesthesia for his obstetrical practice, and as Victor Robinson enthusiastically exclaims, mothers may be indeed grateful to him, for he has taken away their greatest pain, and the birth of a child is now not necessarily accompanied by that acute, tearing agony of the period of labor.

This discovery and the discovery of antiseptics had at once a tremendous influence on the development of surgery. “When I was a boy,” wrote Sir Clifford Allbutt, “surgeons operating upon the quick were pitted one against the other like runners on time. He was the best surgeon both for the patient and onlooker, who broke the three-minute record in an amputation or a lithotomy. What place could there be in record-breaking operations for the fiddle-faddle of antiseptic precautions? The obvious boon of immunity from pain, precious as it was, when we look beyond the individual, was less than the boon of time. With anesthetics ended slap-dash surgery; anesthesia gave time for the theories of Pasteur and Lister to be adopted in practice.”⁶

The teachings of Lister were enthusiastically accepted by a number of surgeons on the continent, and as Garrison says, perhaps the most noted of the surgeons of that time who developed Lister's ideas in new fields was Theodore Billroth (1829-1894). He made the first resection of the esophagus (1872), and, in 1881, the first resection of the pylorus for carcinoma. His visceral work did much to stimulate study in and to clarify the pathology of all abdominal organs. Billroth's contemporaries in Europe and in America were known to many now alive as excellent surgeons, pioneers in the newer operative fields, and enthusi-

astic teachers of their specialty. It needs but to mention the names of Czerny, Thiersch, Von Esmarch, Paget and Hutchinson in Europe, and Bigelow, Gross, Keen, Senn and the Mayo brothers in America, to impress one with the wealth of great names in this field. In Russia, the work of Nikolai Ivanovich Pirogoff (1810-1881) did much to stimulate interest in surgery. He was the first to use ether in military surgery.

In the specialties of surgery, the great advances made during the past century are too numerous to be recounted here in detail. To America belongs the credit of having made the initial advances in gynecological surgery. Ephraim McDowell (1771-1830), of Virginia, a pupil of John Bell of Edinburgh, settled in the wilds of Kentucky and soon became a wonderful surgeon. He performed twenty-two lithotomy operations successively with complete cure, and in 1809 he did the first ovariectomy on a woman forty-seven years old. The initial work of McDowell was continued by James Marion Sims (1813-1883), of South Carolina, who in 1852 perfected an operation for the cure of vesicovaginal fistula, by Thomas Addis Emmet, by Sir Thomas Spencer Wells (1818-1897), by Lawson Tait (1845-1899), by Howard A. Kelly and by others.

The advances in obstetrics, ophthalmology and the other specialties were marvellous. It is sufficient to state that the accomplishments in all the surgical branches since the days of Pasteur, and Lister far outshine the progress made until the middle of the nineteenth century.

Coeval with the great discoveries made in microscopic life, there were made complete revolutions in the conceptions of the animal physiology and of pathology. These studies influenced greatly the progress of clinical medicine, so that in many instances accurate scientific measures were developed in the diagnosis and treatment of sickness. The study of the physiological action of drugs was an attempt to place medicinal therapeutics on a logical basis, and the advances made in pharmacology in recent years bespeak great hopes for this science in the future.

In ancient times the conception of the functions of organs had its basis in mystery and magic, and until the nineteenth century the advances made were those of Harvey, who discovered the circulation of the blood, of Malpighi, who actually demonstrated the connection of arterial and venous capillaries, of Priestley and Lavoisier, who discovered oxygen and described combustion, and of Haller, whose experiments on the phenomena of irritability were correctly performed, although the conclusions drawn therefrom by his followers were deterrent to the progress of science. "In its most complete form, the idea provided for a distinct dualism between living and lifeless matter, making all vital actions dependent upon the operation of a mystical supernatural agency. This assumption removed vital phenomena from the domain of clear scientific analysis, and for a long time exercised a retarding influence upon the progress of physiology." (Locy.)

But during the nineteenth century the whole question of physiology was thoroughly investigated, and a brilliant epoch in the progress of biological science was inaugurated. In 1811 Charles Bell (1774-1842) published a small essay entitled, "Idea of a New Anatomy of the Brain,"

in which he divined by deductive reasoning and not by experimentation that the nerve fibers of the anterior roots of the spinal cord belong to the motor type, while those of the posterior root belong to the sensory type. What Bell arrived at by poetic inspiration, the famous physiologist of Germany, Johannes Müller (1801-1858), proved in the laboratory. Helmholtz, his pupil, says of Müller: "Whoever comes into contact with men of the first rank has an altered scale of values in life. Such intellectual contact is the most interesting thing that life can offer." Though he was a great believer in the vitalistic conception of life—he had contemplated entering the Church previous to his devotion to science—Müller's scientific observations and his breadth of vision led him to make wonderful advances in many of the domains of biology—physiology, psychology, morphology, embryology, chemistry and pathology. We shall enumerate a few of his contributions: his studies on sensations, his discovery of the lymph heart in the frog, his experiments on the vocal cords and the voice, his experiments on the vision and color appreciation, his isolation of chondrin and gluten, and his discovery of the function of the bristle cells of the internal ear, may be mentioned as some of his memorable scientific attainments.

The great pupil of Müller, Hermann von Helmholtz (1821-1894), did much to continue his teacher's work in physiology. In 1840, Müller had stated that no one could measure the velocity of a nervous impulse. Ten years later, Helmholtz had done so. His studies on optics and acoustics are classical. In 1851 he invented the ophthalmoscope, and established ophthalmology as one of the exact sciences. However, his great contribution to science is the universal application of the first law of thermodynamics, that all modes of energy, as heat, light, electricity and all chemical phenomena are capable of transformation from one to the other, but that no energy can be destroyed or created. This, together with the law of conservation of matter, is the solid rock upon which all science is founded.

Of the other German masters of physiology, Carl Ludwig (1816-1895), Du Bois-Reymond (1818-1896) and Hugo Kronecker are those who have shed great luster on the scientific annals of their country.

In France also, simultaneously, there developed a great school of scientific investigation, led by the famous Claude Bernard (1813-1878), to whom Magendie generously conceded, "You are a better man than I." His attitude to science may be summed up in his own words: "Put off your imagination, as you take off your overcoat when you enter the laboratory; but put it on again as you do your overcoat, when you leave the laboratory. Before the experiment and between whiles, let your imagination wrap you around; put it right away from you during the experiment itself, lest it hinder your observing power."

When one opens a textbook on physiology, one is struck with the frequency with which one meets the name of Claude Bernard. He touched every field of this science, and made it much richer for his explorations. The glycogenic function of the liver was described by him in 1857, when he also isolated glycogen. Garrison, in his charm-

ing history, states of this discovery: "The fact that this substance could be obtained, seen as such and experimented with, was more potent even than Wöhler's work in establishing the fact that the animal body can build up chemical substances as well as break them down. Further on, Bernard made it clear that the glycogenic function of the liver is in the nature of an *internal secretion*, a term which he first introduced. 'This,' says Foster, 'at one blow destroyed the then dominant conception that the animal body was to be regarded as a bundle of organs, each with its appropriate functions.' "

His discoveries are too numerous to mention in detail here. He described the glycosuria that follows puncture of the floor of the fourth ventricle, investigated pancreatic digestion, studied the heat regulation of the body, described the vasodilator and vasoconstrictor nerve effects on the circulation, and made very many more contributions to physiology and pharmacology.

The investigation of the physiological chemistry of digestion was inaugurated by Bernard. Previous to him, an American army surgeon, William Beaumont (1785-1853), had studied the nature of the gastric juice and the movements of the stomach *in situ*, in the case of an accidental gastric fistula (1825). In 1834, Johann Eberle suggested that the function of pancreatic juice was to emulsify fats, and ten years later Gabriel Valentin discovered its amylolytic property. But to Bernard belongs the credit of thoroughly studying the digestive influence of the pancreas. He investigated its effects on starch, fats and protein, and demonstrated that it not only emulsifies but breaks up fats into fatty acids and glycerol.

To Bernard's pupil, Willy Kühne (1837-1900), of Hamburg, is due the honor of identifying the proteolytic enzyme of the pancreas, which he called trypsin. But the great Russian physiologist, Ivan Petrovich Pavloff (1849-1916), made the thorough investigations on the chemistry of digestion and the effect of nervous stimulation on the quality and quantity of the juices secreted. He has established a great and fertile school of physiological study at Petrograd and his pupils have given great promise of continuing the excellent work of their master. Pavloff's book on "The Work of the Digestive Glands" is a classic. His experiments are described by him in such simple language that even a layman will easily grasp their significance: "I am also able to demonstrate to you the following instructive experiment: In the presence of some of my hearers, who were invited to attend an hour before the lecture, I carried out the following procedure on two dogs, both of which had ordinary gastric fistulæ, and were, besides, esophagotomized. Into the stomach of the one a definite number of pieces of flesh were introduced through the fistula, the animal's attention being distracted by patting and speaking so as to avoid arousing any thoughts of feeding. The morsels were threaded on a string, the free end of which was fastened into the mouth of the fistular cannula by a cork. The dog was then brought into a separate room and left by itself. A like number of pieces were introduced into the stomach of the other dog in the same

way, but during the process, a fictitious meal was given, the animal being afterwards left alone. Each dog received 100 grams of flesh. An hour and a half elapsed, and now we may draw the pieces of flesh out by means of the thread and weigh them. The loss of weight, and consequently the amount of flesh digested, is very different in the two cases. In that of the dog without the sham feeding, the loss of weight amounts to merely six grams, while the flesh withdrawn from the stomach of the other dog weighs only 70 grams, that is to say, was reduced 30 grams. This, therefore, represents the digestive value of the passage of food through the mouth, the value of a desire for food, the value of an appetite."

The study of the physiology of metabolism was begun by Justus von Liebig (1803-1873) and by Friedrich Wöhler, whom we had occasion to mention previously.

In 1840, Liebig published a dietary study in which an attempt was made to estimate the carbon balance on a company of soldiers. In 1862, Max von Pettenkofer (1818-1901) perfected his respiration apparatus. This furnished a much better means of investigating the respiratory products than any before used. It differed in several essential points from the respiration apparatus which Regnault and Reiset used in their experiments with animals in 1856, or the still earlier form used by Boussingault from 1839-1844. In 1862, Ranke made a considerable number of experiments on man with the Pettenkofer apparatus, and in 1855-66, Pettenkofer, in collaboration with Carl von Voit, who had elaborated and improved the apparatus, published the results of their experiments, which are classical masterpieces on this subject.⁷

The elaboration of a simple method for the determination of nitrogen by Johann Kjeldahl in 1883 did much to facilitate metabolic study, and the work of Pettenkofer and von Voit was continued by Ranke and Max Rubner, Edward Pfleger, and Carl von Noorden in Germany, by Atwater, Chittenden and others in America, by Malfatti, Albertoni and Novi in Italy, by Grandean and Leclerc in France, by Paton and Worth in England, and by the Russian school, whose work is most excellent in this field, and whose names include those of Tchudnovski, Pashutin, Danilevski, Likhachev and many others.

Of the great physiological chemists of Germany, one must devote a few words to the achievements of Felix Hoppe-Seyler (1825-95), of Emil Fischer and of Emil Abderhalden. Hoppe-Seyler is the greatest physiological chemist between the time of Liebig and the time of Fischer. The great contributions of Emil Fischer to our knowledge of the chemistry of proteins and carbohydrates, and of Emil Abderhalden to our conceptions of the specific ferment protective mechanism of the animal body, are of very recent date. Abderhalden is still comparatively a young man, and much additional may be expected from him to the great things he has already accomplished. In America the great living physiological chemists are William John Gies, P. A. Levene, Lafayette B. Mendel, and others.

The brilliant results achieved in the study of the endocrine glands

in the past quarter century are the outcome of the initial experiments of Claude Bernard, who in 1855 described the glycogenic function of the liver as the *sécrétion interne*, in contradistinction to the secretion of bile which he designated a *sécrétion externe*. In the same year appeared the book by Thomas Addison (1793-1860) "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules." This inaugurated the study of diseases of the glands of internal secretion, about which, as Swale Vincent writes, "there has been much loose thinking and loose writing." In 1889, Charles Edouard Brown-Séquard (1817-1894) found that subcutaneous injections of extracts of testis exercised considerable influence upon the general health as well as the muscular power and mental activity. The experiments were performed upon himself when he was seventy-two years old, and he described very marked rejuvenating effects.⁸ He, therefore, promulgated the theory that all tissues give off some unknown substance or substances to the blood, which is specific and particular for each particular tissue, and which plays an important rôle in the general nutrition of the body. "This may be regarded as the real beginning of the modern doctrine of internal secretion, and represents the actual view of many modern writers, particularly in France" (Vincent). Brown-Séquard's contributions are his experimental production of Addison's disease by extirpation of the adrenal glands in animals, his testicular therapy, and his glandular treatment of acromegaly.

Moritz Schiff (1823-1896), a Jewish physician of Frankfort-am-Main, added much to our knowledge of endocrinology. His experiments on the effects of excision of the thyroid in dogs, and the cure of these effects by thyroid grafts and by the injection or ingestion of thyroid extracts, are epoch making. To him is due the great discovery of the treatment of myxedema and cretinism. Sir William Osler pays tribute to Schiff: "A mother brings her child to . . . the neurological department, a poor dwarfed, idiotic creature, but all the same very dear to her heart. It is a far cry from the little laboratory where Schiff made his immortal experiments, and literally thousands of workers in the mines of science have slaved to find the pure gold, handed out freely from this hospital to that poor woman, with which salvation was wrought for her poor child. It seems so easy now. 'Ah, a cretin. How interesting! How old do you say? Eight? Why, she looks three. All right, do not worry, the child will get well quick; get these powders. Yes, three times a day!'"⁹

In 1889, Von Mering and Minkowski described the artificial production of diabetes mellitus by the excision of the pancreatic gland. This was ascribed to the removal of the internal secretion produced by the islands of Langerhans, as shown by the experiments of Opie, of Szoboleff, and of W. G. MacCallum.

The discovery of the effect of adrenal extract by Oliver and Schäfer, the study of thyroid disease by Graves, Basedow, Slemmon and others, the discovery of iodine in the thyroid gland by Baumann, the investigation of parathyroid disease by Sandstrom, Gley, Halsted and others,

of pituitary disease by Mohr, Pierre Marie, Fröhlich, Harvey Cushing and others, of the thymus by Kopp, Richard Bright, Paltauf and others, and of the sexual glands by Paton, Battey and others, have added an interesting and very fruitful chapter to the science of physiology.

The conception of the structural conformation of living tissue was very vague until the late thirties of the last century. Before that time, microscopists had observed, as for example, Hooke of England, Malpighi of Italy, Wolff and Oken of Germany, that organs were composed of small subdivisions, which they called cells, vesicles, utricles, etc., but this was simply an arbitrary observation of the appearance of the structure of living matter under the magnifying glass. No attempt had been made to theorize or generalize on this subject. In 1838, the so-called "Cell Theory" was propounded by the two friends, Matthias Jacob Schleiden (1804-1881) and Theodore Schwann (1810-1882). They demonstrated that all plants and animal tissues were identical in their ultimate structural composition, and they concluded, in the words of Schwann, "that the elementary parts of all tissues are formed of cells in an analogous though very diversified manner, so that it may be asserted that there is one universal principle of development for the elementary parts of organisms, however different, and that this principle is the function of cells." "The development of the proposition that there exists one general principle for the formation of all organic productions and that this principle is the formation of cells, as well as the conclusions which may be drawn from this proposition, may be comprised under the term 'Cell Theory,' using it in its more extended significance, while in a more limited sense, by the theory of cells we understand whatever may be inferred from this proposition with respect to the powers from which these phenomena result."

Max Verworn, the great physiologist of Jena, thus discusses the scientific importance of the work of Schleiden and of Schwann: "It is to the cell that the study of every bodily function sooner or later drives us. In the muscle cell lies the problem of muscular contraction and of the heart beat; in the gland cell resides the causes of secretion; in the epithelial cell in the white blood corpuscle, lies the problem of the absorption of food, and the secrets of the mind are hidden in the ganglion cell."¹⁰

Several years before the announcement of the Cell Theory which so profoundly affected philosophic speculation, Felix Dujardin (1801-1860) had noticed in lower animal life a semi-fluid, jelly-like substance which he called *sarcode*, and which he described as being endowed with all the qualities of life. Schleiden called this substance *gum*, and Hugo von Mohl (1805-1872), a botanist, *schleim*, and Johann Evangelista Purkinje (1787-1869) *protoplasm*. In 1850, Ferdinand Cohn (1828-1898) assumed, and in 1861 Max Schultze propounded the "protoplasm doctrine" to the effect that the units of structure of tissues consist of minute masses of protoplasm surrounding a nucleus, and that this protoplasm is practically identical in plant and animal life.

The effect of the promulgation of the Cell Theory is seen at once

on the Gargantuan strides that the sciences of embryology, histology and pathology made in the immediate decades following; for, scientists reexamined what they had seen before, with broadened vision and more philosophic thought, and found newer wonders and greater marvels in the smallnesses of Nature's workmanship. With Magendie they could exclaim, "*In tota minima Natura est.*"

Karl Ernest von Baer (1792-1876), the greatest of all embryologists, discovered the mammalian ovum in 1827. Almost a century before, Kaspar Friedrich Wolff had shown that the embryo is constructed out of material which is arranged in leaf-like layers (1759), and this observation was more clearly defined by Christian Pander, who, in 1817, showed by experiments on the chick embryo that it was composed of three layers out of which the body was ultimately constructed. It was the great achievement, however, of von Baer that he generalized this observation of his friend Pander, and established it as one of the laws of nature, that these three layers are present in the embryos of all animals, except the very lowest, and that these "germ layers" form all the organs of the body by convoluting to assume the necessary shape and structure. Von Baer had assumed that the "germ layers" were four in number and it was Robert Remak (1815-1865), a Jewish physician, who pointed out that the two middle layers are really a division of one—the mesoderm.

But these morphologic observations were at once made general, when it was discovered in 1861 by Carl Gegenbaur that the ova of all vertebrate animals, regardless of size and condition, are in fact only simple cells. In 1865, this was also proved to be the case of all sperm cells. "The rest was relatively easy: the egg, a single cell [fertilized by a sperm cell], by successive divisions produces many cells, and the arrangement of these into primary embryonic layers, brings us to the starting point of Wolff and von Baer. These cells continue to multiply by division, not only increase in number, but also undergo changes through division of physiological labor, whereby certain groups are set apart to perform a particular part of the work of the body. In this way arise the various tissues of the body, which are in reality similar cells performing a similar function. Finally, from combination of tissues, the organs are formed."¹¹

The work of these pioneers in embryology was extended by Rathke and Remak in the fields of invertebrate and vertebrate zoölogy. In 1866, Kowalevsky (1840-1901) demonstrated that there is no definite division between the vertebrate and the invertebrate animals, so far as their development goes, for he showed similar stages of development in the case of the Amphioxus (considered an invertebrate) and a tunicate. "The Recapitulation Theory," foreshadowed in the writings of von Baer and of Louis Agassiz, was clearly enunciated by Fritz Müller in 1863. According to this theory, "animals are supposed, in their individual development, to recapitulate to a considerable degree phases of their ancestral history." This theory is enthusiastically advocated

in the writings of the great English embryologist, Francis Maitland Balfour (1851-1882), and of the German biologist, Ernest Haeckel.

Virchow made the general dictum, "*Omnis cellula e cellula*." The characteristics of the parent cells are transmitted to their offspring, and it is upon this fact that the modern theories of heredity are based. In 1866-67, Gregor Mendel (1822-84) studied by experimentation—remarkable in a monk!—the effect of inheritance on the individual characters in twenty-two varieties of garden peas. He cross-bred pure races, showing certain constant physical characteristics, as for example, color, length of stem, seed conformation, etc., and produced hybrids. He then proceeded to observe the results of self-fertilization among these hybrids. He then enunciated the following law, known as the Mendelian Law: "Whenever there occurs a pair of differentiating characters, of which one is dominant to the other, three possibilities exist: there are recessives which always breed true to recessive character; there are dominants which breed true to the dominant character, and are, therefore, pure; and, thirdly, there are dominants which may be called impure and which on self-fertilization (or in breeding, where the sexes are separate) give both dominant and recessive forms in the fixed proportion of three of the former to one of the latter" (R. C. Punnett).

This dictum of Mendel and the work of Francis Galton (1822-1911), a cousin of Charles Darwin, have founded the science of Heredity, from the study of which the future will, no doubt, greatly benefit. Galton studied the inheritance of stature, and other characteristics in human families and formulated the law of ancestral inheritance, published in 1889: "The parents together contribute one-half of the total heritage, the four grandparents together one-fourth, the eight great-grandparents one-sixteenth, and all the remainder of the ancestry one-sixteenth."

Another result of the advancement of the Cell Theory was the progress made in microscopic anatomy, or histology. Foremost in the ranks of histologists, we must mention the name of Jacob Henle (1809-1885). Garrison writes of him: "Altogether, the histological discoveries of Henle take rank with the anatomical discoveries of Vesalius." He was of Jewish descent, born in the town of Fürth, near Nuremberg, and was one of Johannes Müller's favorite pupils. Scientists concede him to be the greatest German histologist of his time and one of the greatest anatomists of all time. We can only sum up his contributions to science in a few words, for his awe-inspiring books fill a shelf in the library. He studied the character of the epithelial cells of the skin and all mucous membranes, pointing out their similarity; described the involuntary muscle-fibers in the tunica media of the blood-vessels; gave an accurate account of the histology of the cornea; pointed out important new facts in the brain anatomy, pituitary structure, kidney histology (Henle's tubules), etc. Contemporary with Henle, the greatest histologists were Remak and Purkinje, and Albert von Kölliker (1817-1895), who studied under Henle.

Franz Leydig (1821-1908) applied histology especially to the tissues of insects. Two brilliant scientists have done great work in this field.

One, Ramon y Cajal, is a Spaniard, and the other, Camillo Golgi, is an Italian. Their special contributions have been in the study of the microscopic anatomy of the nervous system.

The founder of cellular pathology is Rudolph Virchow (1812-1902). He was a man of revolutionary ideas not only in science but also in political reform, so much so, that in the upheaval of 1848 he had to flee Prussia. Upon the recommendation of Scanzoni, he obtained the chair of pathologic anatomy at Würzburg. His teacher had been the great Johannes Müller, who, besides him, had for his pupils that great and famous list of men, Brücke, Henle, Wagener, Helmholtz, Bois-Reymond, Claparede, Ludwig, Schwann, Volkmann, Reichert, Lachmann, Vierordt, Kölliker, Remak, Lieberkuhn, and Haeckel—a company of scientists whose names have left unerasable impressions on the sands of time.

Virchow was in reality the spiritual successor of the Frenchman, Marie F. X. Bichat (1771-1801), of whom Thomas Henry Buckle, the historian, writes: "It is from this point of view that we are to rate the value of Bichat, whose words, like those of all men of the highest eminence—like those of Aristotle, Bacon and Descartes—mark an epoch in the history of the human mind." The German pathologist proved that all cells come from parent cells, and this was the foundation of his treatise on tumors. Virchow was the first to describe leukocytosis and to point out that condition of the blood characterized by the afebrile increase of white blood cells, which he called leukemia. He demonstrated that the important phenomenon of embolism is the primary cause of phlebitis, whereas it had been previously conceived that phlebitis gave rise to thrombus formation. He described arthritis deformans, studied the histology of the neuroglia, and discovered the lymphatic sheaths of the cerebral arteries.

The greatest pupil of, and successor to, Virchow was the Jewish scientist, Julius Cohnheim (1839-1894). His experiments on inflammation and suppuration were epoch making in pathology. In opposition to his teacher, he demonstrated that diapedesis of leukocytes is always present in inflammation. His experiments on tuberculosis, and on the nerve endings in muscle, and his introduction of newer pathological methods will always be considered as monumental contributions to this science. He was a very great teacher, and among his pupils may be mentioned Heidenhain, Ehrlich, Neisser, Weigert, Welch, and Councilman.

Carl Weigert (1845-1904) is another of the great pathologists of the last century. His methods of staining bacteria by anilin dyes, his investigations in renal disease, smallpox, pathology of nervous system and veins are memorable.

The further progress of pathology is so intertwined with the advances made in clinical medicine, that we shall refer to the contributions to pathology by the great clinicians in giving the story of some of the great practitioners of the latter times.

Medicine during the first half of the nineteenth century was in a restless state, and schools upon schools arose, practicing their own

fads and fancies, so that Virchow, in 1854, indignantly exclaimed: "German Medicine, on account of its views and dissenting schools, has become the laughing stock of the world." Oertel has graphically described the situation of the time.¹² "There did not exist a well-founded universal scientific method of thought, investigation or teaching, but only opposed and battling 'schools' and 'systems' of Hahnemann, polygramasia, Rademacher's system, Priessnitz's system, therapeutic nihilism, eclecticism, Bouilland's bleeding to unconsciousness of the patient, Dietl's absolute condemnation of bleeding as a criminal offense (1849), mesmerism and others. They formed the source of senseless and endless discussions, for they were all speculative and contributed much to the entertainment of their pompous defenders and the laity, but not to the benefit of their patients. . . . It was not even a time of crude empiricism, but a fantastic period, which, like a nightmare in individuals, occasionally arises during the life of a nation."

When one reads this, one is shocked when reminded that in one state of our own country, more than ten so-called "schools of medicine" are permitted to practice their foolish and ignorant, if not criminal, theories on the credulous, misled, and misinformed public.

But toward the latter half of the nineteenth century, the advances made in the laboratory began to show the result of their influence on the practice of the healing art.

In Germany, in France, in England, in the United States, and in the other European and American nations there have been established clinics and hospitals in connection with universities or with research laboratories, where eminent clinical teachers met their students and demonstrated and discussed the art and the science of medicine. In the Teutonic countries, Friedrich Theodor von Frerichs (1819-1885) was especially famous as an instructor and practitioner. He was a great teacher, and delighted especially in the autopsies which formed part of his clinical instruction. He is famous for having discovered the crystals of leucine and tyrosin in the urine of a patient suffering with acute yellow atrophy of the liver, for his studies in the pathology of hepatic disease, and for his work on diabetes. In the Introduction to his first volume of "Diseases of the Liver," Frerichs wrote: "Clinical and practical medicine have made a difficult stand in opposition to the results arrived at by modern means of scientific research. . . . A large proportion of medical men are upholders of the system of practice transmitted from the ancients. They have regard solely to the empirical method of treatment, and take little cognizance of medical science. They look upon this as something extraneous from which they select what is practically useful, or what may serve for assisting diagnosis, or for the elucidation of individual symptoms, or some kindred purpose, but their general views are not at all influenced by it."

The great clinical teachers of Germany include Kussmaul, Traube, Ziemssen, von Leyden, Nothnagel, Senator, Naunyn, von Noorden, and many others of international repute. Adolph Kussmaul (1822-1902) contributed much to our knowledge of diabetic coma, osteomyelitis,

bulbar paralysis, mesenteric thrombosis and many other important subjects. Ludwig Traube (1818-76), one of the great Jewish physicians, was an ardent experimentator in pathologic anatomy. His writings on pulmonary disease, febrile states, suffocation, digitalis, and vagus physiology are justly famous.

In England, William Withey Gull (1816-90). Samuel Wilks (1824-1911), Fagge, Golding Bird, Thomas Clifford Albutt, and others have been famous clinical teachers and writers.

America and England both boast of Sir William Osler, for while he was a Canadian by birth, he spent the most productive years of his life teaching at the University of Pennsylvania and at Johns Hopkins University. In 1904, the mother country called him to her famous seat of learning, and until his death (1920) in his seventieth year he was Regius Professor of Medicine at the University of Oxford. As a writer of attractive English, as an excellent teacher of Medicine, as a brilliant diagnostician, and as a charming medical historian, there are few in England or America that can rival this master of medicine. Other great American physicians are Emanuel Libman, William Sidney Thayer, and Frank Billings.

In psychology and psychopathology great advances have been made in the last five decades. Among the leaders in this science are Pierre Janet. Alfred Binet, Adolph Meyer, von Krafft-Ebing, Havelock Ellis and others. A great step forward has been taken in the conceptions of hysteria and in the "psychopathology of every-day life," by the work of the Jewish physician, Sigmund Freud of Vienna. His writings are epoch making, and he has found many exponents of his teachings, in men like A. A. Brill, W. A. White, and J. J. Putnam of America.

In the study of therapeutics and of physiology a new science was developed, that of pharmacology. Huge steps have been taken in the study of the action of drugs on the animal economy, but very much more work is to be done to make this an exact learning. It seems that there is a relationship—some claim a definite one—between the constitution of a substance and its physiological effect, so much so, that Emil Fischer made a deliberate attempt (1904) to produce a reliable hypnotic and synthesized veronal.

The greatest German pharmacologist is Oswald Schmiedeberg, a pupil of Rudolph Buchheim (1820-1879). He was the first to study the action of poisons on the frog's heart. Contemporary with him are Karl Binz (1832-1912) and Hans Meyer, in Germany. In America the work of Wood, Abel, Hunt, Sollmann and Samuel James Meltzer are noteworthy. The famous pharmacologists of England are Sir Thomas Lauder Brunton and Arthur Robertson Cushny.

With the dawn of modern chemistry, the developments of methods for the medicolegal recognition of poisoning reached a very high point, though as Witthaus states, "It is far short of what it will attain in the future." According to this great toxicologist, there are six events in the history of toxicological chemistry which mark important stages in the development of this science: The first of these is the practical ap-

plication of the previously observed properties of hydrogen arsenid to the detection of arsenic, by James M. Marsh (1836), whose technic, though modified, is still the basis of all delicate tests for arsenic. Then, in 1839, Orfila extracted notable quantities of arsenic from the liver, spleen, kidneys, heart and muscle of the assassin-suicide Soufflard, this being the first instance of the extraction of *absorbed* arsenic from the human cadaver. Five years later, Fresenius and von Babo developed a process for the systematic investigation for all mineral poisonings. So far as organic toxicology goes, the separation of the vegetable alkaloids from medicinal and poisonous plants, beginning with the studies of opium by Sertürner (1805) marked a new departure in toxicology and pharmacology. Stimulated by the necessity for isolating nicotin in a case of suspected poisoning, Stas, in 1851, devised a scheme for the separation of alkaloidal poisons from the cadaver, which, though modified, is still in general use. In 1874, Selmi demonstrated that the substance which had been extracted from an exhumed body and which was supposed to be morphin upon analysis, was in reality not morphin but a putrid product, a ptomain or a "cadaveric alkaloid."¹³

"Medicine," says Professor Vaughn, "consists of the application of scientific discovery to the prevention and cure of disease. All else which may go under the name of medicine is sham and fraud." The public authorities, aided by the advice of the medical profession, can save more lives by the prevention of disease than by permitting the disease to develop and endeavor to have it cured later. It is this principle that has almost eradicated typhoid fever in the community, made small-pox a rare disease, and cholera an unknown affliction. The installation of systems of filtered water and good sewerage, the passage and enforcement of laws tending to regulate the building of residences for the poor, the control by the local health board of persons suffering with contagious disease and the free distribution of small-pox vaccine, diphtheria and tetanus antitoxin have done more to lower the mortality list than the use of the "senna and rhubarb" of the therapist. It is to prophylaxis of disease that the future generation will owe its safety.

The great German physician, Max von Pettenkofer (1818-1901), inaugurated the science of experimental hygiene. He studied the effects of various diets on the health, the influence of ventilation of dwelling houses, methods for the estimation of carbon dioxid in the air, the relation of atmosphere to clothing, and the relative advantages of stove and hot-air heating of homes.

The government now regulates the health surroundings of the working people, and stringent laws are passed to secure for the laborers sanitary shops and homes. Industrial hygiene will do much to eradicate disease and alleviate poverty among the working classes. In most civilized countries, children under puberty are not allowed to work in the factories, and, while in certain states of the Union a benighted spirit still reigns supreme, Congress is attempting, by heavy taxation, to force these southern states employing child labor to forego this method of exploitation.

Comparable to all the great advances of the past century is the progress made in the establishment of modern hospitals where women do the ministering work to the sick. For, in this noble pursuit, womanhood has attained its most beneficent influence to the community. Women serve now to lessen the suffering of the sick, to attend to his personal comforts, and console him in his great pain and grief.

It was Theodore Fliedner (1800-1864), a pastor, who originated the idea of training women in the care of the ill. His idea was originally to teach discharged female prisoners how to go about the sick. But it is to the great Englishwoman, Florence Nightingale (1823-1910), to whom the credit is due for establishing a teaching institution where noble-hearted women could be taught how to take care of those that suffer with bodily ailments. During the Crimean War (1854), she went out with a body of nurses to minister to the sick and wounded brought in from the battlefield. Since then, women play as important a rôle in war as men, for, while the soldier aims only to destroy and kill, the nurse helps the physician in reclaiming the injured and crippled from death.

The future of medicine is in the advancement of the scientific work done in the laboratory. There are still a number of fossilized minds who cling to the idea of "vitalistic conceptions of life," and, while they may retard science for a while, they and their obstructive tactics will disappear, for science must finally triumph. It has been pointed out by the eminent Jewish biologist, Jacques Loeb, in his masterly book on "The Materialistic Conception of Life," that all vague vitalistic theories will have to yield to the positive demonstrations of scientific truth. "*Eppur si muove*," murmured to himself Galileo, who had just recanted his life-long sought truth, and the monks and fools that surrounded him were pleased with the untruth which they had forced from the aged, kneeling sage. But the times are changed. There may be those who would wish for the power to command the "Sun to stand still upon Gibeon, and thou, Moon, in the Valley of Ajalon." The miracles of the day of Joshua are, however, passed, and neither the Sun of Science nor the Moon of Meditation will halt in their glorious path of ultimate liberation of the world from moral and political and physical disease.

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CHAPTER VI

HYPERSENSITIVENESS

By ARTHUR F. COCA, A.M., M.D.

Definition, p. 107—Classification of the phenomena of hypersensitiveness, p. 108.

Anaphylaxis, p. 110—Exciting agents of anaphylaxis, p. 110—Active sensitization, p. 117—Passive sensitization, p. 118—The symptoms and pathology of anaphylaxis, p. 124—Local anaphylaxis, p. 136—Antianaphylaxis, p. 138—Antisensitization, p. 142—Theories of the mechanism of anaphylactic shock, p. 143.

Allergy, p. 154—Definition, p. 154—General allergic symptoms, p. 154—Drug allergy, p. 156—Serum allergy, p. 162—Hay-fever, p. 179.

Tuberculin sensitiveness, p. 185.

Toxin hypersensitiveness, p. 191.

Definition.—If an individual reacts specifically or particularly, with characteristic symptoms, to the administration of, or to contact with a quantity of any substance, which, to the majority of the members of the same species of animal, is innocuous, that individual is said to be “hypersensitive” to that substance.

The feature of “specificity” or particularity is an important criterion in the definition of hypersensitiveness. It depends, in one group of the phenomena of hypersensitiveness (“anaphylaxis”), on the specificity of the antibodies, which are responsible for that condition. The particularity exhibited in another large group of the phenomena of hypersensitiveness—that which we shall designate as “allergy”—is, in many instances at least, not referable to an immunological process, since the exciting agents are not capable of inducing the production of antibodies. The cause of this particularity is not known; its superficial resemblance to immunological specificity has led to frequent confusion of the phenomena of allergy with those of anaphylaxis.

By “characteristic symptoms” is meant a symptom-complex that is generally different in the different animal species for the same group of substances but uniform in any one species for various substances. Furthermore, the symptoms of “hypersensitiveness” under the proposed definition are different from those elicited by the *normal physiological action* of the respective material.

It is evident that the definition, which has just been given, of “hypersensitiveness” is out of agreement with its etymological derivation, because the assertion of a condition of hypersensitiveness in one individual presupposes a condition of normal sensitiveness in other individuals, whereas certain substances to which “hypersensitiveness” exists, notably horse serum, pollens or their extracts and foodstuffs, are entirely in-

nocuous to most persons or animals when administered in the usual manner and in ordinary amounts. However, since the term hypersensitiveness has so long been used in the sense of the foregoing definition, and as there seems to be no more accurately descriptive word that could be used in that sense, it appears wise to retain the term, notwithstanding its inconsistent etymological derivation.

The definition of hypersensitiveness that is here proposed excludes from that category the phenomena of toxin-hypersensitiveness and tuberculin sensitiveness; the former because its symptoms are not different from those of the normal effect of the toxins, the latter because its symptoms are the same in all animals and because they are different from those of hypersensitiveness to any other substance in any animal. However, these two phenomena will be briefly treated in separate chapters.

Classification of the Phenomena of Hypersensitiveness.—The consideration of the subject of hypersensitiveness has been rendered difficult because, through the disregard of the one restricting criterion of the condition of anaphylaxis, many experimental and also clinical phenomena having a superficial or even a closer resemblance to those of anaphylaxis have been included in this category. This complication is increased by the wide and stoutly maintained differences of opinion as to the nature and site of the anaphylaxis reaction itself and even to differences as to conception of the underlying immunological processes. (Vaughan.)

Doerr^(a) has realized the necessity of an orderly classification of the phenomena of anaphylaxis and of those phenomena that have been associated with them, based on clear definition of the terms employed, and he has attempted to meet this need.

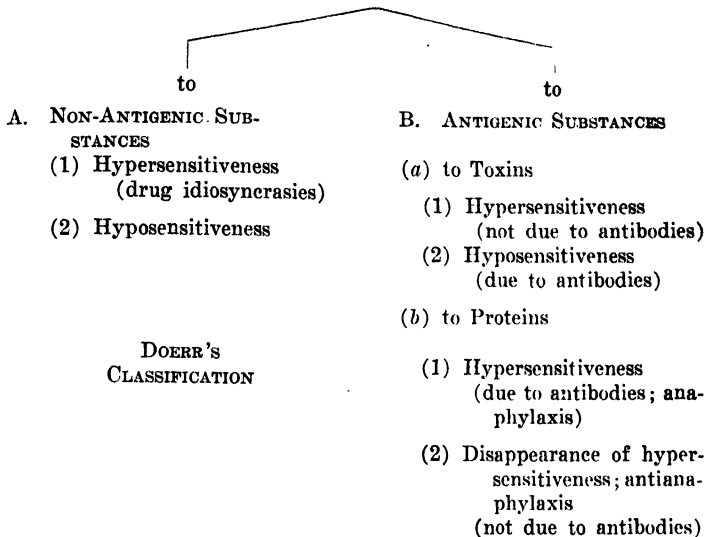
Doerr has extended the application of the term *allergy*, which had been restricted by its author, von Pirquet, to the designation of altered reactivity resulting, as he believed, from immunological processes. Doerr made the word *allergy* include all of the phenomena of altered reactivity of whatever nature, adding the phenomenon of hyposensitiveness to the original one of hypersensitiveness as a criterion of altered reactivity.

Doerr's classification is given on the opposite page. There are two objections to Doerr's classification:

First, in including the various phenomena of hyposensitiveness in the consideration of the subject of altered reactivity, Doerr has added, in every case, phenomena whose etiology is different from that of any of the forms of hypersensitiveness. This association does not contribute anything to the understanding of the processes of hypersensitiveness, and it may even tend to obscure such understanding.

Secondly, the separation of the phenomena of altered reactivity according to the nature of the exciting agent (that is, with reference to antigenic property) must, for the present, at least, result in a subdivision of the etiologically related phenomena of natural human hypersensitiveness, since the exciting agent in some instances of this cate-

ALLERGY



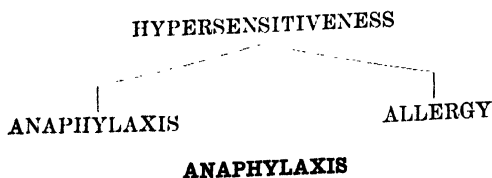
gory (those of drug idiosyncrasy) is not of antigenic nature, whereas in other cases (those, for example, of hypersensitiveness to animal proteins) the exciting agent appears to be an antigen.

Since no advantage to the understanding of the present subject is gained, indeed, quite the reverse, in considering the etiologically unrelated phenomena of hyposensitiveness, the term *hypersensitiveness* becomes available as an inclusive term upon which to build a classification. It is proposed, therefore, to consider the phenomena of hypersensitiveness in two categories; the first to include only those that have been shown to be due to the interaction of antigen and antibody—the hypersensitiveness of *anaphylaxis*; the second to embrace all other forms of hypersensitiveness (as defined above); that is, those in which the co-operation of true antibodies has not been demonstrated. For the latter category is reserved the term *allergy*.

It will be seen that the phenomena which the proposed definition assigns to the class of allergy, though elicited by so wide a variety of substances, have many more features in common than the merely negative one of an unproved antigen-antibody mechanism. Indeed, the marks of similarity are so numerous and so close that the burden of proof must be placed on those who would assume that the *etiological basis* is not *identical in all of them*. Thus, although the proposed use of the term allergy represents a considerable restriction of its etymological significance (altered reactivity), this restriction is amply justified, and particularly so by the greatly enhanced importance with which

the term will be invested if the conception of an identity of mechanism underlying all of the manifestations of allergy can be upheld.

The proposed classification is, then, simply:



Anaphylaxis is a state of hypersensitiveness that is due to the presence, in certain tissues, of specific antibodies, the symptoms of anaphylaxis being caused by the meeting of these antibodies with the respective antigen in those tissues.

The conditions under which the meeting of antibody and antigen must take place in order to produce the symptoms of anaphylaxis vary, in part, in the different animal species. However, one of the necessary conditions is common in all species, namely, that the union of the antibodies with the whole of the minimal fatal amount of the antigen must take place within a definite brief space of time. In other words, if that minimal amount of antigen, as determined by intravenous injection, is injected in such a manner (as by the subcutaneous route or very slowly by the intravenous route) that all of it does not arrive at the site of the antibodies within a definite period of time, the symptoms of anaphylaxis are lessened in severity or they may be entirely absent.

. AGENTS AND MODES OF ANAPHYLACTIC SENSITIZATION

Exciting Agents of Anaphylaxis (*Anaphylactogens*).—The state of anaphylaxis can be induced only by antigenic substances. However, since not all antigenic substances are capable of inducing the state of anaphylaxis, there is need of a term designating only those antigens which are capable of inducing that state, and this need has been met with the term "*anaphylactogen*."

An *anaphylactogen* is an antigenic substance that is capable of inducing, in the animal body, a condition of specific hypersensitiveness, which, through the mediation of the induced antibodies, when these are present in the blood of the treated animal, can be transferred to a normal animal.

This definition excludes from the category of anaphylactogens all of the non-antigenic chemical substances that are the exciting cause of the drug idiosyncrasies, as well as some of the active principles concerned as exciting agents in the "human sensitizations," such as those in hay-fever and in the idiosyncrasy to strawberry, since these active principles seem, also, to be lacking in antigenic property. It excludes, also, the

true toxins, for the reasons given in the discussion of toxin hypersensitiveness (see page 191).

The anaphylactogens, without exception, are proteins, the experiments with lipoids, carbohydrates and other non-proteid substances resulting either negatively or unconvincingly.

All of the anaphylactogens are proteins whose reactions with their specific antibodies are characterized by phase alteration (agglutination, precipitation) and also by changes in the medium of the reaction, as indicated by the phenomenon of complement-fixation. It happens that the antibody reaction of the antigens that are not anaphylactogens, that is, the toxins, is not accompanied by either perceptible phase alteration or complement-fixation, and this fact possibly accounts for the failure of the toxins to induce anaphylaxis. Whether the phase alteration of the protein-anti-protein reaction is actually of importance in anaphylaxis is, however, not known.

All of the attempts to refer the anaphylactogenic function and the other known antigenic functions to different elements in the same proteid material have failed; indeed, there is strong direct evidence of the identity of the anaphylactogenic and the precipitinogenic elements in such material. Furthermore, the precipitinogens appear to be identical with the elements that give rise to the complement-fixing amboceptors.

As the specificity of the reaction expressed by the symptoms of anaphylactic shock has been found to agree with that exhibited with the other immunological reactions, such as those of specific precipitation and complement-fixation, the technic of the anaphylaxis reaction has been largely employed in the study of the phenomenon of specificity.

The question of immunological specificity resolves itself into that of the chemical constitution or physicochemical condition of antigenic substances.

As exclusive use has been made of the guinea pig in the study of this question the succeeding statements apply only with respect to that animal.

It has been found to be a general requirement of physical state that the anaphylactogenic substance be in solution * or capable of dissolving in the body fluids after injection. Such anaphylactogens as are coagulable by heat lose their anaphylactogenic property progressively under the influence of that agent, as more and more of the molecules pass into the irreversible gel condition of coagulation.^(a) Under these circumstances since the sensitizing amount of the anaphylactogens is usually but a very small fraction of the quantity required to elicit the symptoms of anaphylactic shock, the heated material loses its power to shock the sensitized animal long before its sensitizing property is finally extinguished. That it is alone the coagulating effect of heat which deprives the coagulable proteins of their anaphylactogenic property is indicated by the fact that this property is not affected in non-coagulable

* By solution, here, is meant, of course, colloidal dispersion, as all anaphylactogens are colloidal substances.

References: (a) 14, 34, 81, 82, 107, 134, 135, 203, 265, 266.

anaphylactogens, such as milk or ovomucoid, by prolonged boiling.^(a) The requirement of solubility applies, also, to the formed antigens such as blood-corpuscles, inasmuch as the latter exercise their sensitizing function only after they have been dissolved in the tissues of the injected animal.

The anaphylactogenic property is modified or entirely suppressed by numerous chemical methods and other physical agents; for example, ozonization,^(b) treatment with osmic acid^(c) or with ultraviolet rays,^(d) conversion into acid albumin or alkali albuminate.^(e) The sensitiveness of the antigenic function to chemical change is seen in the fact that it is greatly reduced in even the earliest digestion products of the original material. Animals that have received injections of the material at the stage of the "primary albumoses" are brought to only a moderate degree of hypersensitiveness (the tested animals usually died after 12 hours), which is the same whether the digestion products or the original material is used for the test injection.^(f) Thus, the deterioration of the antigenic function of the original material caused by the proteolysis does not involve a change in its specificity that could be interpreted as corresponding with the alteration in the chemical structure of the protein molecule. However, it should be mentioned here, that Wells, injecting ox serum that had been subjected to trypsin digestion, observed a more intense shock in animals sensitized with the digestion product than in those sensitized with the unchanged ox serum.

The question of the structural basis of antigenic specificity has been studied with the aid of the precipitin reaction in the well-known experiments of Obermayer and Pick,^(g) who found that, by the introduction into the protein molecule of iodine or the nitro- or diazo-groups, the species or biological specificity was suppressed and was replaced by a specificity which was determined by the substituted chemical group. Contrary to the expectation, the results of those experiments received but scant confirmation in the subsequent studies that were carried out with the use of the anaphylaxis reaction. With this technic, the alterations in the antigenic property of proteins, that could be detected as a result of the chemical procedures referred to, were generally identical with those produced by the various physical agents and other chemical methods of treatment mentioned above. In short, with few exceptions, the antigenic function was progressively weakened but not affected as to its biological specificity by the introduction of iodine into the molecule. Schittenhelm and Stroebel,^(h) in their investigation of iodized serum and iodized egg-white with the use of the technic of anaphylaxis, reached the conflicting conclusion that while, contrary to Obermayer and Pick, the iodized egg-white retains its biological specificity, yet it exhibits an acquired iodine specificity, as indicated by its interaction with iodized ox serum. This complication was increased by their further observation that an animal previously treated with iodized ox serum

References: (a) 266 (see also 204, pp. 22-37). (b) 210. (c) 51. (d) 79, 80. (e) 266. (f) 285. (g) 185. (h) 210.

was killed with an injection of iodized Witte pepton. The authors admit the marked irregularity of the results in the treated animals, yet they content themselves with relatively few control tests of the preparations employed (22 test animals and 5 control animals). The method of passive transfer was not used.

In view of the conflicting or inconclusive results thus far obtained with the technic of the anaphylaxis method, the problem of antigenic specificity cannot be considered as solved by the chemical substitution method introduced by Obermayer and Pick.

On the basis of his study of the "protein poison" discovered by him, Vaughan has proposed a theory of anaphylactogenic function, which he applies in the explanation of the phenomena of anaphylaxis and also of those of infection. Vaughan has found that from most proteins of vegetable or animal origin can be obtained by treatment with an alcoholic solution of alkali, a poisonous product, which, according to Edmunds^(a) and others, causes symptoms like those of anaphylactic shock. This "protein poison" lacks anaphylactogenic property, whereas that function may be detected in the non-toxic residue that results from the process employed by Vaughan.^(b) The latter observation forms the original ground of Vaughan's theory according to which the protein molecule consists of a central, non-specific, toxic, chemical nucleus, attached to which are secondary chemical groups that carry the function of specificity.*

The parenterally administered protein excites, according to Vaughan, the production of specific ferments, that are capable of splitting the protein molecule at the point of union of the central and the secondary groups, thus giving rise to a toxic product, and it is this mechanism which underlies the symptomatology of anaphylactic shock.

The theory of Vaughan is vitiated by a weakness that is inherent in the basic observations—a weakness that has been obvious in all of the experimental attempts to separate a sensitizing substance from an intoxicating substance in anaphylactogens. The theory is dependent upon the assumption of Vaughan and Wheeler^(c) that the process with which the protein poison is produced causes a splitting of *all of the molecules* in the material subjected to it, and this assumption is proved, according to the authors, by their observation that the non-toxic residue sensitizes animals against the original protein but not against itself. The fallaciousness of such evidence lies in the demonstrated fact that the amount of protein required to sensitize a guinea pig is but a minute fraction of the amount necessary to intoxicate or to desensitize the sensitized animal. The argument should, indeed, be reversed; we should look upon the sensitizing property of the non-toxic residue as conclusive evidence that intact traces of the original material still remain in it. These traces, in the light of the results obtained by Vaughan and Wheeler, were sufficient to sensitize guinea

* Vaughan makes antithetical use of the terms anaphylactogen and antigen, the former being applied, by him, only to proteins, the latter only to the true toxins.

References: (a) 88. (b) 230. (c) 230.

VOL. I.—8.

pigs, but they were not sufficient, in the amounts injected, to desensitize nor to intoxicate. Thus, the experiments of Vaughan and his co-workers can not throw any light on the structural basis of specificity.

Zunz,^(a) falling into the same error of interpretation on the basis of his observation that a preparation of synalbumose derived from ox serum sensitized to other (ox serum) proteoses and to the original material but not to itself, concludes that the amino-acid group in the proteose molecule that is responsible for the sensitization is not the same as the one which is responsible for or necessary to the production of anaphylactic shock.

Direct evidence concerning the question of structural specificity was sought in the study by Gay and Brailsford Robertson^(b) on the antigenic properties of "globin-caseinate," which is a compound of globin (the histon-like body derived from hemoglobin) and casein. These authors found that repeated injections of globin alone into rabbits were not followed by the production of demonstrable antibodies. However, in the serum of animals injected with globin-caseinate complement-fixing antibodies were found for both globin and casein as well as for these two substances in combination. Gay and Robertson interpret these results as indicating that the property of specificity is exercised independently by chemical groups in the protein molecule.

Since this interpretation must rest on the assumption that the combination of globin and casein designated by Robertson as "globin-caseinate" represents a chemical union of the two constituents, it should be borne in mind that such an assumption is not warranted by the available information regarding combinations of this kind. The studies of the constitution of the class of compounds of which Robertson's globin-caseinate is a member have not revealed even presumptive evidence that such compounds represent true chemical combinations of the component proteid substances.

The true explanation of the above-mentioned observation of the authors—that the otherwise non-antigenic globin acquires antigenic property when combined with casein—may be a physical one instead of a chemical one. It is conceivable, namely, that the lack of demonstrable antigenic power in the isolated globin is due solely to its insoluble state, and this assumption is supported by the observation of Gay and Robertson that guinea pigs that have been sensitized with the "globin-caseinate" are sensitive to casein and to globin-caseinate, but not to globin alone. As Derr suggests, the failure of the animals to react to globin may be due to the insolubility of this substance in the alkaline blood fluid. It is, furthermore, conceivable that in its combination (which may be a purely physical one) with casein, globin remains, when injected into animals, in a more soluble condition than when injected alone, and thus comes into such intimate contact with the susceptible tissues as to stimulate the production of specific antibodies.

However this may be, it appears proper to withhold judgment as

to the interpretation of these experimental results until the nature of the globin-casein combination is clear.

The idea that antigenic specificity resides independently in chemical groups within the molecule has been adopted by Wells and Osborne^(a) in their study of the antigenic relations of purified vegetable proteins. These proteins were either chemically related but derived from different sources; e.g., gliadin of wheat and rye and hordein of barley; or they were chemically different but derived from the same source, e.g., gliadin and glutenin of wheat.

The significant experimental results were as follows:

(1) Hordein and the gliadins of both wheat and rye "interacted"; that is, guinea pigs sensitized to one of these proteins could be shocked by the injection of either of the other two proteins.

(2) Animals sensitized with one of the two substances, hordein or wheat gliadin, and subsequently desensitized to the other substance, still retained their hypersensitiveness to the substance used in the sensitization, and that to only a moderately diminished degree.

(3) Gliadin and glutenin of wheat interacted and, moreover:

(a) Animals sensitized with glutenin were sensitive to both of the gliadins but not to hordein.

(b) Animals sensitized to glutenin reacted more intensively to an injection of the gliadin of wheat than to one of glutenin; furthermore, the reaction of the glutenin-sensitized animal to gliadin was somewhat more severe than that caused by the injection of gliadin into a gliadin-sensitized animal (compare the authors' Table 3).

(c) Animals sensitized with wheat gliadin appear to react somewhat more vigorously to an injection of wheat glutenin than to one of wheat gliadin; furthermore, the reaction of the gliadin-sensitized animals to glutenin is evidently more severe than that caused by an injection of glutenin into a glutenin-sensitized guinea pig.

(d) Animals sensitized with wheat glutenin and entirely desensitized to the same material appear to remain sensitive to wheat gliadin.

(4) Animals sensitized with wheat glutenin react vigorously to wheat gliadin, though considerably less so to rye gliadin and not at all to hordein. On the other hand, glutenin-sensitized guinea pigs are partially desensitized by all three of these substances, the desensitization with hordein being quite as marked in degree as that produced with either of the gliadins.

The main theoretical conclusions drawn by Wells and Osborne from their experiments were:

(1) The specificity of the anaphylaxis reaction is determined by the chemical structure of the reacting proteins rather than by their biological origin.

(2) It seems probable that the entire protein molecule is not involved in the specific character of the anaphylaxis reaction, but that this is developed by certain groups contained therein and that one and the same protein molecule may contain two or more such groups.

They say, however, "Until we have some means whereby the chemical individuality of a protein can be established the possibility will remain that our so-called pure preparations of proteins consist of mixtures, or combinations of proteins which have thus far resisted all efforts to separate them."

The second conclusion of the authors (the one under present discussion) rests wholly on the belief that each of their preparations contained only one protein substance. However, the methods of separation employed by Wells and Osborne offer, as they admit, no guarantee of individual isolation of the proteins with which they worked. Indeed, separation methods based upon solubility relations as applied to colloidal substances are notoriously unreliable, and it is just such methods that were used by these investigators.

The paradoxical results obtained by Wells and Osborne in the cross-tests and particularly in the cross-desensitizations appear to be most easily explained with the assumption of a mixture of proteins in the different preparations. The small amount of gliadin contaminating the preparation of glutenin and vice versa is, perhaps, absorbed by the larger bulk of the predominating substance, and in that condition it is physically less altered by the process of purification; the absorbed protein may thus have retained an original power of intensive sensitization that otherwise is modified by the purification process. The minute amount of the contaminating protein is sufficient to sensitize the guinea pig, though not sufficient completely to desensitize the animal against itself.

The results of the cross-desensitization experiments demonstrate, as the authors point out, common antigenic principles in hordein and the two gliadins and they show a like relationship between glutenin and the two gliadins. It is noteworthy that the relationship of wheat glutenin to wheat gliadin is distinctly closer than it is to the gliadin of rye, although Wells and Osborne state that the two gliadins are identical in their biological reactions (cross-desensitizations with the two gliadins are not recorded).

Wells and Osborne conclude, from their cross-tests with glutenin and hordein, that no common antigenic principles are present in these two preparations. If this is so, then it must seem unlikely that the interaction of wheat gliadin and glutenin is due merely to a mutual contamination. However, the results of the glutenin-hordein cross-tests present an internal contradiction, which makes them unavailable for the settling of this point. It appears that, although guinea pigs that have been sensitized with glutenin show no hypersensitiveness to hordein, yet they can be partially desensitized to glutenin by injections of hordein. Confusing irregularities are recorded, also, in the desensitization experiments with animals sensitized with hordein.

If it is true that glutenin-sensitized animals, after thorough specific desensitization to glutenin, remain sensitive to wheat gliadin (and this interpretation of the respective cross-tests is accepted by Wells and Osborne), then it must be admitted that the group sensitization

to gliadin was not induced in the animals by any component of glutenin. The phenomena may be satisfactorily explained by the assumption of a gliadin contamination of the glutenin preparation in amount sufficient to sensitize but not to desensitize. However, the contradictory results of the experiments with the hordein-sensitized animals make doubtful the interpretation of the finding that we have just discussed.

The theoretical importance of the question involved makes an extension of these experiments appear desirable.

The preceding review of the experimental facts bearing on the problem of antigenic specificity makes those facts appear inadequate to a satisfactory solution of the problem.

Active Sensitization.—The process of active sensitization depends on the previous introduction into the cell-complexes of the body of the undigested anaphylactogen and such introduction can be *parenteral*, as by any of the routes of injection (for example, subcutaneous, submucous, subconjunctival, subdural, intraperitoneal, intravenous or intra-ocular), or, rarely, it may be *enteral*, traces of the anaphylactogen having, under such circumstances, passed unchanged into the circulation through the normal or, more often, injured gastro-intestinal mucous membrane. In some instances active sensitization in guinea pigs appears to have resulted from the passage of the anaphylactogen through the intact conjunctival and respiratory mucous membranes. The latter observations have offered an explanation of the hypersensitiveness that is exhibited by the symptoms of hay-fever.

The optimal number of the sensitizing injections varies with the different species of animal, a single one sufficing for guinea pigs and dogs, a more constant result being obtained in the mouse and the rabbit by repeated injections.

The minimal amount of the antigenic substances required for active sensitization varies greatly with the different species of animal and somewhat also, with the different antigens. Guinea pigs have been actively sensitized with as little as 0.000,01 to 0.000,001 c.c. of serum or 0.000,000,05 gram of crystalline egg albumen. Rabbits require, for active sensitization, from 1,000 to 10,000 times as much of the same material as do guinea pigs.

INCUBATION PERIOD OF ACTIVE SENSITIZATION.—The period of time that must elapse after the primary administration of the antigen before the condition of hypersensitiveness can be established varies with the species of animal, the amount of the antigenic material introduced, and the route of its administration as well as the method of testing the hypersensitiveness. The shortest incubation period observed in the guinea pig was 5 days; in the dog hypersensitiveness does not appear until 2–3 weeks after a primary injection of 3–5 c.c. of serum.

The smaller the amount injected into guinea pigs, the longer the incubation period; an interval of 19–25 days is required for the development of hypersensitiveness after the injection of 0.000,1–0.000,01 c.c. of ox serum.

Intracerebral injection seems to be followed in guinea pigs, some-

what sooner—7 days—than subcutaneous injection—9 days—by hypersensitiveness, while in the rabbit the response appears to follow after enteral administration more quickly than after any other mode.

The earliest appearance of the hypersensitiveness can be detected with the intravenous test injection; at this time intraperitoneal injections, in any amount, usually fail to cause symptoms of anaphylaxis.

The simultaneous injection of more than one antigen in equal amount does not influence the incubation period of the active sensitization to the different antigens. If, however, a relatively large amount of one antigen is injected 24 hours previous to the usual sensitizing injection of a second antigen, the incubation period for the latter substance is markedly increased.

The duration of the active hypersensitiveness resulting from a single injection of horse serum is strikingly different in guinea pigs and in rabbits, the latter losing the hypersensitiveness after about three weeks,^(a) the former remaining fully sensitive for years.

THE TEST INJECTION OR "REINJECTION."—This may be made by subcutaneous, subdural, intracardial, intraperitoneal or intravenous routes, the last two being usually preferred. The intravenous injection in rabbits offers no difficulty; this procedure in the guinea pig requires the service of an assistant and it is best performed with the use of a platinum needle of 22 gauge bent or curved near the tip to an angle of about 110 degrees, the animal being firmly strapped to an inclined operating board such as that recommended by Friedberger.

Passive Sensitization.—In the blood fluid of animals immunized against an antigenic proteid substance can be demonstrated a specific antibody, which, when injected into a normal animal in suitable amount, confers on the latter a state of specific hypersensitiveness similar to that of active anaphylaxis.^(b) The differences between this passive form of anaphylaxis and the active form (for example, the shorter duration of the former) are largely attributable to the foreign quality of the sensitizing antibodies in passive sensitization, the transferred antibodies being quickly destroyed in the recipient. The remaining differences are chiefly of a quantitative nature, being due, in this respect, to the unlimited controllable variation in the passively sensitized animal, in the amount of the sensitizing or "anaphylactic" antibody that may be present.

Anaphylactic sensitization can be passively transferred to individuals of the same species or to those of different species. Doerr has collected the following list of positive and negative results in the attempted heterologous passive sensitization:

Positive results:

Man	to	guinea pig
Monkey	to	" "
Rabbit	to	" "
Dog	to	" "

References: (a) 58, 219. (b) 199, 200, 198, 187, 102.

Positive results:

Cat	to	guinea pig
Horse	to	" "
Guinea pig	to	rabbit
Chicken	to	pigeon

Negative results:

Birds	to	mammalia
Mammalia	to	birds
Rabbit	to	white mouse
Guinea pig	to	" "

It is a striking fact that the conditions governing passive sensitization differ radically, in one respect, in the different animal species. This difference has to do with the influence of time interval (following the transfer) on the sensitization. In the guinea pig, on the one hand, the transfer of the antiserum, whether of homologous (of the same species) or heterologous (of a different species) origin, is not followed immediately by the establishment of hypersensitiveness, a certain period of incubation (4 to 6 hours) being required for the development of that condition. Passive sensitization, once established in the guinea pig, persists for a considerable period, which is much larger after the use of a homologous immune serum (60-70 days) than after the use of a heterologous immune serum (about 10 days).^(a) In the rabbit and in the dog, on the other hand, passive hypersensitiveness supervenes at the moment of the injection of the antiserum.^(b) In the rabbit the passive hypersensitiveness is of short duration, disappearing, according to Friedmann, within 24 hours after the transfer,^(c) in the dog it has been reported to persist for 20 days.^(d)

In considering the question of the duration of passive hypersensitiveness, it must be borne in mind that especially after a large injection of the antigen into the prospective donor, the blood of the donor may contain not only antibody but also small amounts of the antigen, which are specifically unrelated to the circulating antibody. If such persisting traces of circulating antigen are transferred to the normal animal, an active sensitization will be induced and this may occur before the passive sensitization has disappeared.

The earliest explanation, which was offered by Doerr and Russ, for the latent period of passive anaphylaxis in the guinea pig, was that it indicated the period in which the antibodies, on which the sensitization depends, were entering into an essential relation with the body cells.^(e) However, with the later general acceptance of the humoral conception of anaphylactic shock, this explanation fell into oblivion and it was replaced, for a time, by one designed to place the phenomenon of the latent period of passive sensitization on a humoral basis.^(f) This explanation assumed a qualitative change in the transferred antibodies, which was designated as an "activation." Later studies^(g) demon-

References: (a) 247. (b) 219, 155. (c) 103. (d) 198. (e) 81. (f) 40. (g) 249, 59.

strated the incorrectness of the latter view, since it could easily be shown that if, at the end of the latent period, the blood of the passively sensitized animal is transferred to another normal animal, the latter, likewise, becomes passively hypersensitive but not without an incubation period of exactly the same duration as that of the first transfer. In other words, the quality of the antibodies, with respect to the latent period of passive sensitization, shows not the least change. Antibody "activation" does not take place during that period.

These studies have, thus, exposed a fatal weakness in all humoral conceptions of anaphylaxis, which the followers of such theories have made no further effort to eradicate. The results point to the original explanation of Doerr and Russ as the only one compatible with the facts.

The events of the latent period of passive sensitization in the guinea pig have been studied, with exact quantitative methods, by von Fenyvessy and Freund.^(a) These experimenters determined, with a maximal error of 10 per cent., the minimal sensitizing dose of antisera (chiefly homologous), using guinea pigs of approximately constant weight (about 300 grams) and administering the passively sensitizing serum by intravenous injection. After varying intervals of time following this sensitizing injection, a number of the animals that had received the minimal sensitizing dose of antiserum were bled to death and the sera thus obtained were pooled. To a quantity of this pooled serum that was calculated to have contained, immediately after the sensitizing injection had been given, one minimal sensitizing dose of the antiserum; that is, a quantity representing the total volume of serum in one guinea pig, to this was added either $\frac{1}{3}$ or $\frac{1}{2}$ or $\frac{2}{3}$ of a minimal sensitizing dose of the antiserum and each of these mixtures was injected into a normal guinea pig. From the results of the test injections made into this latter series of animals could be estimated the fraction of a minimal sensitizing unit which had been withdrawn by the fixed tissues from the blood of the original passively sensitized animal previous to the time at which it was bled to death.

These estimations indicated that after one hour only 20 per cent. of the single minimal sensitizing dose of antibodies had been withdrawn from the circulation of the injected animal; after 4 to 11 hours, 40 per cent. was missing, and after 24 hours only 50 per cent. of the single unit had been withdrawn. After three days 25 per cent. of the sensitizing antibodies could still be demonstrated in the blood.

It is evident, if, after 11 hours (at which time the passively sensitized guinea pig is fully sensitive) the tissues have withdrawn only 40 per cent. of the single sensitizing dose of the antibodies, that only a fraction (not more than one-half) of the antibodies, injected in the single sensitizing dose, enter into the reaction which is responsible for the anaphylactic shock induced at that time. This conclusion is based on the well-founded assumption that the circulating antibodies take no part in the reaction of anaphylaxis, except to interfere with it.

Reference: (a) 238.

In explanation of the foregoing observations, von Fenyvessy and Freund assume that a certain concentration of the sensitizing antibodies in the blood is required to enable the tissues to absorb sufficient antibodies for the establishment of a fatal degree of passive sensitization. However, the observations may be explained, also, by the assumption, for which there appears to be some suggestive experimental support,* of more than one sensitizing antibody (precipitin) in antiprotein antisera, one of which is endowed with a greater avidity in combining with the antigen and is, perhaps, more quickly taken up by the tissues.

Von Fenyvessy and Freund found, furthermore, that if, one hour after the injection of one sensitizing unit of antiserum, 40 to 50 per cent. of the passively sensitized guinea pig's blood was withdrawn by bleeding, the animal, notwithstanding this calculated loss of 32 to 40 per cent. of the injected antibodies, nevertheless, became fully sensitized after the usual period.

The authors assume, from this observation, that the 20 per cent. of the injected antibodies, which they had shown to be removed by the fixed tissues from the circulation at the end of one hour, represents the whole of the fraction necessary for the sensitization. However, since the state of sensitization is not established until five or six hours after the injection of the antiserum, it seems necessary to assume, further, that the sensitizing antibodies, after they have been removed from the blood by the fixed tissues, must be subjected to another change, the nature of which is unknown.

The question as to the relation of the antibodies responsible for the hypersensitiveness of anaphylaxis to the antibodies, demonstrable with the criterion of specific precipitation, is closely associated with the question as to the relation of the anaphylactogenic and the precipitinogenic substances.

That the latter are identical appears to have been clearly established by Doerr and Moldovan,^(a) who found that both of these functions disappeared from a quantity of ox serum that was capable of actively sensitizing 100 guinea pigs when it was mixed with a precipitating antiserum in proper proportions. Weil,^(b) on the other hand, was able to identify anaphylaxis antibody, which he designated with the term "sensitizin," and precipitin by passively sensitizing guinea pigs with the washed specific precipitate obtained by mixing a precipitating antiserum with small quantities of the respective antigen.

Other evidence of this association of the two antiprotein antibody functions in one substance had been obtained in the demonstration of a constant parallelism in the course of antibody production in the rabbit^(c) and the guinea pig,^(d) as determined with the test-tube and the animal experiment.

While the uniformly successful passive sensitization with washed specific precipitates, in Weil's hands, permits no further doubt as to the

* This volume, page 140. (See discussion of Weil's experiments in partial desensitization (Antianaphylaxis).)

References: (a) 78. (b) 256. (c) 264, 83, 138. (d) 7, 99.

identity of precipitin and "sensitizin," there are some recorded observations that demonstrate certain differences between the function of specific precipitation and that of anaphylactic sensitization in the anti-protein antibodies, as well as some hitherto unexplained discrepancies between precipitin and "sensitizin" content of the blood of immunized animals.

Burekhardt ^(a) showed that, as compared with the quantitative relations of the serum of a guinea pig four days after the last antigen injection, the precipitin content remained apparently unchanged until after the 14th day, whereas by that time the passively sensitizing power of the animal's blood had distinctly diminished.

Von Dungern and Hirschfeld ^(b) treated a precipitating serum with Lugol's solution and found that whereas its precipitating power was only slightly diminished by such treatment, its sensitizing power was greatly lessened.

Finally, it has been shown by Weil ^(c) that the precipitating function of antiprotein antibodies can be suppressed in three different ways (by heating the diluted antiserum for one-half hour at 70° C.; by mixing the antiserum with an excess of antigen—prozone; and by extracting the antibody from a specific precipitate with sodium carbonate) without corresponding suppression of their sensitizing function. These facts invite further study.

Since the passively sensitizing power of an injected animal's serum resides in the contained specific antibodies, the amount of such serum required to produce a certain degree of passive sensitization depends on the concentration of the antibodies in it.

The quantity of circulating antibody in an injected animal depends in part on the quantity of the antigen injected, in part on the number of injections, and in part on the length of the period of time within which the injections are given. Thus, in a considerable percentage of guinea pigs that have received the single small injection of egg albumen usually made in the active sensitization of these animals, the presence of circulating antibodies cannot be demonstrated, while in the serum of the remainder of the animals the antibodies are found in relatively low concentration. On the other hand, a single larger injection or several injections made within the latent period of active immunization, that is, before the first appearance of antibodies, are less effective in antibody production than the usual process of immunization—several injections made at intervals of five or more days. Naturally, if so large an injection (for example, 30 c.c.) is given that the injected material cannot be absorbed and eliminated before the altered immunological reactivity of the antibody-producing tissues has taken place (4th or 5th day) the effect of antibody production will be the same as that of a repeated injection given after that interval.

The conditions governing the process of passive sensitization differ in the guinea pig and the rabbit, not only as to the period of incubation, to which reference has been made, but also as to the quantity of

the antibodies required. The quantity of a rabbit's immune serum that is required passively to sensitize a rabbit is relatively much greater than the minimal sensitizing quantity for a guinea pig.

In the study of the problems of anaphylaxis in all of its relations constant use has been made of the technic of passive sensitization, and the most satisfactory combination, in this respect, has been found to be the one originally recommended by Doerr and his co-workers, namely, the active immunization of the rabbit and the passive transfer of the antibodies thus obtained to the guinea pig. The advantage of this combination is twofold; for, on the one hand, the rabbit excels the other laboratory animals in antibody production and, on the other hand, the guinea pig is perfectly adapted to the quantitative study of both antibody and anaphylactogen by means of the anaphylaxis reaction. Guinea pigs of equal weight that have received identical amounts of a sensitizing antiserum present an almost identical degree of hypersensitiveness to the respective antigen. That is, usually all will be killed or nearly killed, by the intravenous injection of the same minimal amount of the antigen.

Doerr and Russ ^(a) have proposed three methods for the determination of the relative concentration of the sensitizing antibodies in immune serum. These methods have not been subjected to a sufficient number of parallel tests with the same sera to permit conclusions as to whether the results obtained with the three methods are always concordant. At any rate, the second one to be mentioned appears to be available for the usual practical purpose of such determination, that method being most commonly employed.

The three methods are:

(1) Each of a series of guinea pigs of an average weight of 250 grams receives an intraperitoneal injection of 1.0 c.c. of the antiserum. After 24 hours the minimal fatal dose of the anaphylactogen for the series is determined by intravenous injection. Under the method, the smaller the determined minimal lethal dose of the antigen the greater the estimated antibody content of the immune serum.

(2) A series of 250-gram guinea pigs receive varying amounts (1.0 to 0.05 c.c.) of the antiserum by intraperitoneal injection and after 24 hours they are tested with the intravenous injection of a constant larger amount of the antigen.

(3) A constant quantity (1.0 c.c.) of the immune serum is mixed, in a series of test-tubes, with varying amounts of the antigen, and each mixture is injected intraperitoneally into a normal guinea pig of 250 grams weight. After 24 hours the guinea pigs are tested with an intravenous injection of a constant larger amount of antigen. The smaller the amount of antigen with which neutralization of the sensitizing antibodies is accomplished, as judged by the absence of sensitization in the guinea pigs, the greater the estimated antibody concentration in the tested serum.

As Doerr himself says, these methods are all arbitrary; however,

Reference: (a) 81.

they are not more so than the ones employed in the test tube estimation of antiprotein antibodies with the criteria of specific precipitation and of complement-fixation.

An insight into the question of the reliability of the information obtainable with the first method is, perhaps, afforded by the following experiment reported by Weil: ^(a)

Guinea pigs passively sensitized with 0.05 c.c. of an immune serum were killed with the minimal amount of 0.05 c.c. of the antigen; animals passively sensitized with 50 per cent. more antiserum could be killed with almost correspondingly (40 per cent.) less antigen. However, a further increase of 33 $\frac{1}{3}$ per cent. in the amount of antiserum used for the sensitization resulted in a decrease of 90 per cent. in the minimal fatal dose of the antigen.

According to these results, it would seem to be not permissible to estimate the relative amounts of antibody used for passive sensitization from the corresponding minimal lethal dose of the antigen.

THE SYMPTOMS AND PATHOLOGY OF ANAPHYLAXIS

The symptoms of the typical, acutely fatal shock of anaphylaxis vary markedly in the different species of animals and these differences in the symptoms have been found to correspond, in the main, with differences in the pathological changes that occur in anaphylactic shock in the respective species.

Acute Anaphylactic Shock in the Guinea Pig.—**SYMPTOMS.**—The sensitized guinea pig that has received a typically fatal intravenous injection of the antigen presents the following symptoms: released immediately after the injection, the animal may be quiet for a minute or it may begin, at once, to run about, evidently excited, pausing at times to scratch itself on the nose or ears and sometimes discharging urine and feces. Within $\frac{1}{2}$ to 2 minutes (sooner, according to Doerr, ^(b) in passively sensitized animals) the guinea pig coughs with a violently convulsive effort several times or jumps convulsively without coughing, then staggers about a few seconds with arched body (sometimes with elevated nose), and finally falls over, making violent rhythmical extension movements of the back and hind extremities accompanied by similar violent movements of the inspiratory musculature of the chest, mouth and nose. The tracing of the intrathoracic pressure during this period ^(c) shows an occasional true convulsion. From this point, the symptoms are purely those of asphyxia, the terminal series of respirations being highly characteristic. These are well described, as follows, by Auer: ^(d) "At first slow and of fair strength, (they) rapidly become swifter and weaker, and finally disappear about one minute after their onset—as the respirations weaken the opening of the mouth and the dilatation of the nostrils decrease, and they, also, disappear. The order of stoppage is first the respiration, then the opening of the mouth and finally the inspiratory widening of the nostrils."

PATHOLOGY.—If the chest of a guinea pig is opened after the cessation of the terminal series of respiratory movements, the heart is found to be still beating regularly and strongly, though there is present a condition of "heart-block,"^(a) the auricles beating two or three times to every ventricular beat. The arterial blood presents the dark color of cyanosis. There is no demonstrable interference with the pulmonary circulation.

The dominant pathological finding is the inflated condition of the lungs noted by Gay and Southard and shown, by Auer and Lewis, to be the immediate cause of death in acute anaphylactic shock in the guinea pig. The inflation not only remains maximal after removal of the lungs from the chest but it resists reduction with moderate pressure. This condition of the lungs was believed, by Auer and Lewis, to be due to a tetanic contraction, peripheral in origin,^(b) of the smooth musculature of the bronchioles (secondary and tertiary) and their explanation of the phenomenon has been amply supported by the subsequent direct demonstration of the hypersensitiveness of the smooth muscle tissue of other organs.^(c) The mechanism of the supposed valve-like action of the bronchial closure, which is thought to be aided by a folding of the mucous membrane, has not been made clear, though it would seem to be a mere expression of the known greater strength of the inspiratory musculature as compared with that of expiration.

The phenomenon of lung-inflation is not encountered in the dog nor in the rabbit, though Doerr^(d) mentions having occasionally seen a condition in the latter animal comparable with an emphysema bullosum.

The production of the lung-inflation in the guinea pig seems to be due not alone to the localization of the antibody-antigen reaction in the bronchial musculature, since the underlying tetanic contraction of these elements is brought about by a number of agents that have no demonstrable relation to anaphylactic shock, such as peptone, histamin, pilocarpin, barium chlorid, sodium hydroxid, copper sulphate, saponin, morphin, oleic acid, acetic acid, colloidal silicic acid and hypertonic sodium chlorid solution. As these substances do not cause lung-inflation in other animals, the guinea pig's bronchial musculature would seem to be particularly susceptible to any irritant. Thus, the absence of this symptom in other animals in acute anaphylactic shock by no means proves the absence of the irritating mechanism of anaphylaxis in the smooth muscle tissue of those animals. That mechanism may, though present, be merely unable, in those animals, to produce the physiological effect that it causes in the guinea pig.

Acute Anaphylactic Shock in the Rabbit.—**SYMPTOMS.**—The symptoms of acute anaphylactic shock in the rabbit are most constantly produced by the following course of treatment: two injections of one or two cubic centimeters are given by the subcutaneous or peritoneal route at an interval of five days. Three days after the second injection daily intraperitoneal or intravenous injections of 0.2 c.c. are made over a period of two weeks or more, and five days after the end of this period

References: (a) 22, p. 171. (b) 213, 15. (c) 217, 215, 216, 67. (d) 76.

the test injection of 2.0 c.c. is made into the marginal vein of the ear.

The animal sometimes remains quiet for about two minutes, then it suddenly begins to run about aimlessly until stopped by wall or furniture, when it falls over, still making running movements, with its head thrown backward. After a few seconds the animal becomes quiet and, with a few short gasps, dies with the eyes in exophthalmos. There is nothing in the behavior of the animal that is in the least suggestive of the intense dyspnea of the guinea pig which has been described; there is no indication, in other words, of any interference with the normal passage of air through the respiratory organs.

The symptoms of the acute shock of anaphylaxis in rabbits may lack the initial excitement, its place being taken, sometimes, by a somnolent state interrupted by an occasional starting up. The terminal stage, however, is identical with that described above.

The blood-pressure, unlike that in the dog, rises, at first, moderately, then, after a minute, it slowly sinks to a few millimeters of mercury, the heart-beat becoming progressively slower. Loewit found the initial rise of pressure to be of central origin, it being missed if the test injection was made after section of the spinal cord.

PATHOLOGY.—Corresponding with the differences in the symptomatology of anaphylaxis in the two animals, the pathological findings in the rabbit dying in anaphylactic shock are different from those in the guinea pig. If the chest of the rabbit is opened immediately after death the right side of the heart is found to be filled with blood, the ventricles not beating or beating very weakly and the auricles beating, in some instances, slowly and regularly.^(a) Instead of being inflated, as in the guinea pig, the lungs are collapsed. If artificial respiration is carried out, the inflation and deflation of the lungs occur with not the least abnormal hindrance.

Auer^(b) called attention to the behavior of the heart in the shocked rabbit, pointing out peculiar changes in the consistence of the muscle substance of the right ventricle, which were absent in the left ventricle. By isolating the heart and lungs from central nervous and splanchnic influence, Auer^(c) was able to prove the peripheral origin of these changes, which he believed to be the immediate cause of death in the rabbit. In a later study with Robinson,^(d) he suggested a causal relationship between anaphylactic processes and heart disease in human beings.

Auer's belief that the heart lesions described by him are of primary origin received experimental support in the observations upon the hypersensitiveness of the isolated heart of sensitized rabbits and guinea pigs.^(e) However, more recent experiments^(f) indicate that the effects noted by Auer in the heart are, in part, secondary to an obstruction of the pulmonary circulation.

It has been found that, whereas the normal pulmonary vascular system of the rabbit can be readily perfused with physiological saline solution under a pressure of 10 cm. of that solution, the same system of

References: (a) 274. (b) 18, 19. (c) 18. (d) 23. (e) 109, 54, 140, 284. (f) 60.

the rabbit dead in anaphylactic shock resists the perfusion of saline solution under much greater pressure, as much as 90 cm., or more, failing, sometimes, to force the least fluid through the vessels. If, in such a case, under the maximal pressure, the lung is cut near the pleural surface, no fluid oozes from the cut surface. The obstruction is, thus, on the arterial side of the pulmonary circulation. A deeper cut allows a slow oozing of the perfusion fluid from the cut ends of the arterioles, a free flow occurring only when the larger branches of the pulmonary artery are severed.

In view of the demonstration, by Auer, of the peripheral origin of the symptoms of acute anaphylactic shock in the rabbit, the assumption seems justified that the obstruction in the pulmonary circulation is due to a tetanic contraction of the muscular coat of the pulmonary arterioles.

Whether, in acute anaphylactic shock in the rabbit, there is a similar spasm in the systemic arterioles has not yet been experimentally established. That such a possibility should be considered is indicated by the fact that a subcutaneous injection of the antigen into the sensitized rabbit produces a local necrosis (gangrene), which points to a local interference with the circulation. Naturally, the systemic action of the antigen in the acute shock would depend, in part, upon the amount of the antigen that passes the pulmonary arterioles before these vessels are completely obstructed.

The congestion of the liver and the lowered coagulability of the blood, which Weil^(a) refers to as occurring in anaphylactic shock in the rabbit, would seem to point to a participation of the liver in rabbit anaphylaxis. However, the mechanical obstruction to the pulmonary circulation, which is constantly demonstrable, offers an adequate explanation of the fall of blood-pressure in the anaphylactic shock in this species.

Acute Anaphylactic Shock in the Dog.—SYMPTOMS.—Previous to the appearance of the last contributions of Weil, acute anaphylactic shock had been rarely observed in the dog on account of the usual employment of a single sensitizing injection. Dogs so treated generally recovered from the test injection or died only after several hours. Weil found^(b) that two sensitizing injections of 5 c.c., the first being given subcutaneously, the second intravenously after an interval of several days, induced a degree of hypersensitiveness such that the test injection of 20–30 c.c. of the serum, given intravenously after a second interval of several weeks, regularly caused almost immediate symptoms and death within 30 minutes. The symptoms of this acute shock in dogs are described by Weil as follows:

“The dog immediately vomits or retches, and generally has a number of evacuations of the bowels. Within five minutes it begins to stagger and to drag its hind legs. Following this preliminary stage comes a period of severe collapse, which, as a rule, appears within ten minutes

of the injection. The animal lies on its side and does not respond to any stimulation. Some animals show at first either a fine tremor of the muscles of the extremities, or a coarse clonus composed of short excursions. These soon cease, and the animal is practically immobile, except for the respiratory movements. Respiration is either shallow and rapid, or labored, and gives the impression of marked dyspnea. During this stage which terminates, usually within thirty minutes, with the death of the animal, the other characteristic features of anaphylaxis make their appearance. The blood pressure sinks so low that the carotid pulse can scarcely be detected. If blood is aspirated from the veins, it is found to have lost its coagulability to such an extent that it remains fluid for several days."

PATHOLOGY.—The exclusive importance of the liver in anaphylaxis in dogs was established by Manwaring,^(a) whose conclusions have been thoroughly confirmed.^(b) It is now known that if the dog's liver is excluded from the portal circulation by means of the Eck fistula the animal thus treated does not become sensitized^(c) after the subsequent intravenous injection of 1.0 c.c. of egg-white, which regularly sensitizes normal dogs. Complete exclusion of the liver from the circulation by compression of the abdominal aorta and of the inferior vena cava just below the diaphragm,^(d) or, after establishing an Eck fistula, by temporary compression of the hepatic artery,^(e) entirely prevents the production of anaphylactic shock in sensitized dogs and, furthermore, the shock does not develop if the compressed hepatic artery is released 10 minutes after the injection of the antigen.

The primary pathological changes in acute anaphylactic shock in the dog are, thus, to be sought in the liver and they have been found to consist chiefly in a congestion of that organ,^(f) as a result of which Weil calculated that about 60 per cent. of the entire extrahepatic blood quota was retained in it.^(g) That the congestion is due to a purely local process was shown by Weil by injecting the antigen into a branch of the portal vein, whereupon only that portion of the liver that was supplied by the selected branch became congested.

The fall of blood-pressure and the incoagulability of the blood, which, with the marked leukopenia, constitute the most constant symptoms of anaphylactic shock in the dog, were first described by Biedl and Kraus.^(h) Because of the shock inhibiting influence of adrenalin and of barium chlorid, the fall of blood-pressure was thought by these investigators to be due to an effect of the anaphylaxis reaction on the nervous mechanism supplying the abdominal vessels.

This view was controverted by Pearce and Eisenbrey,⁽ⁱ⁾ who observed the occurrence of typical anaphylactic shock in the dog after complete exclusion of all nervous influence upon the abdominal vessels. With the use of gutta percha capsules applied to the spleen, kidney and intestine, and by the insertion of cannulae into the right common iliac

References: (a) 155. (b) 231, 71. (c) 71. (d) 155. (e) 231. (f) 259, 260, 261. (g) 260, pp. 542-543. (h) 38. (i) 190.

vein and the inferior vena cava these investigators found that, with the fall of blood-pressure in anaphylactic shock in dogs, the volume of kidney, intestine and spleen decreased as did that, also, of the brain and of the right extremity. On the other hand, the volume of the liver visibly increased and the abdominal veins became engorged with blood. This venous engorgement, which they considered to be due to a "lack of tone, in the vessels of the splanchnic area," was thought, by Pearce and Eisenbrey, to be a sufficient explanation of the shock of anaphylaxis in this species.

Weil,^(a) focusing his attention on the liver as the demonstrated primary site of the anaphylactic reaction in the dog, believed that the accumulation of blood in the abdominal veins was merely the result of obstruction in the liver to the portal circulation, and he considered this effect to be only a contributing cause of the lowered blood-pressure, which was mainly due, he thought, to the retention, by the liver, of the calculated large proportion of blood referred to above. The actual retention of blood by the sensitized dog's liver after injection of the antigen was demonstrated by Weil and Eggleston^(b) in perfusion experiments on the isolated liver.

That the incoagulability of the blood in the dog in anaphylactic shock is due to a cellular reaction in the sensitized liver was made highly probable by experiments, also by Weil,^(c) in which, after the establishment of an anastomosis between the carotid artery of a normal dog and the portal vein of a sensitized dog, the antigen was introduced into the flowing blood by injection through the wall of the connecting rubber tubing.

Whereas, before the introduction of the antigen, the blood, collected, after its passage through the liver, at the opening made in the vena cava above the diaphragm, clotted in 3 minutes, its coagulation time, in one experiment, was increased, after the injection of the antigen, to 13 minutes. In a second experiment the perfused blood, after the introduction of the antigen, remained unclotted after 24 hours.

Summary of Acute Anaphylactic Shock.—The foregoing review of the symptoms and pathology of acute anaphylactic shock presented by the three species of animal in which this condition has been chiefly studied, make it apparent that the phenomenon of anaphylaxis can no longer be looked upon as a single pathological entity, since the mechanism of the injurious effect of the reinjection is totally different in the three species.

The guinea pig dies, in acute anaphylaxis, of asphyxia brought about by a tetanic contraction of the bronchial musculature, which completely blocks the passage of air into and out of the lungs. Such effect is absent in both rabbit and dog.

The rabbit, in acute anaphylaxis, is killed by the complete mechanical interruption of the blood circulation in the arterioles of the lung. This effect has not been noted in either dog or guinea pig.

In the acute anaphylaxis of the dog, death appears to be due to a

References: (a) 260. (b) 263. (c) 260, p. 534.

VOL. I.—9.

sudden accumulation of the greater part of the animal's blood in the liver and in the abdominal veins, the latter being caused by obstruction of the portal circulation in the liver.

Protracted Anaphylactic Shock in the Guinea Pig.—The injection of a sublethal amount of the antigen in sensitized guinea pigs may produce mild symptoms, which soon disappear, leaving the animal in an apparently altogether normal state. The milder symptoms consist of restlessness, erection of the hair, coughing (or sneezing), discharge of urine and feces, and scratching of the head or body. More severe symptoms, though sometimes of short duration, generally take a protracted course. These are those of the initial stage of the fatal acute shock, the dyspnea not reaching the intense degree seen in the latter. Up to this point and especially in those animals that recover quickly from the sublethal dose, the difference between the lethal and sublethal shock appears to be merely quantitative. In some of the animals, however, the initial acute stage of the sublethal shock is followed by a stage of depression characterized by a somnolent state, in which the reflexes are maintained, there being no true paralysis.

It had been observed that when death did result after the protracted form of shock in the guinea pig, as is regularly the case following the peritoneal injection of a lethal dose, the lungs were less inflated than is the case in acute shock.^(a) For this reason the symptoms of the stage of depression and the ultimate fatal issue were not ascribed to pulmonary changes, and Dale has, therefore, suggested that the later phenomena of the protracted shock in the guinea pig are referable to a mechanism (in the liver) identical with that which underlies the similar symptoms in the dog. The notorious risk attached to assuming an identical cause for two similar physiological effects, especially when these are observed in different animal species, seems lessened, here, by the statement of Weil^(b) that in anaphylactic shock in the guinea pig the liver actually becomes congested. However, confirming observations on this point would seem desirable and, moreover, it should not be overlooked that, according to Auer,^(c) even in sublethal shock the lungs are always, at least in part, inflated, and that the degree of inflation in barely lethal, protracted shock appears to be inversely proportional to the duration of the time interval between the test injection and the death of the animal. It seems not impossible—there is no evidence to the contrary—that even the symptoms of the protracted shock in the guinea pig are caused by a slow asphyxia due, perhaps, to a complete bronchial closure in a large portion of the lung, with a partial closure in the remainder.

The protracted shock in guinea pigs is accompanied by a marked fall of body temperature, and this symptom has been recommended as a reliable, objective, quantitative criterion of the degree of the shock,^(d) particularly in animals that present no other symptoms, and ultimately recover.

Injection of smaller amounts of the antigen into sensitized animals may cause, instead of a temperature drop, a rise of body temperature, which, by attention to time interval and dosage, may be made, with repeated injections, to follow the course of the different known types of fever.^(a) This phenomenon will be referred to again under the topic of infections.

Protracted Anaphylactic Shock in the Rabbit.—The rabbit, in protracted anaphylactic shock, presents an increased rate of respiration and a state of weakness resembling, somewhat, the depression of the later stage of the protracted shock in the guinea pig. Death may occur after a varying length of time, the animals that survive for days or weeks usually presenting a condition of cachexia (loss of weight), which, together with local effects that are to be described, has been designated as the phenomenon of Arthus.

It has been found that the pulmonary circulation in rabbits dying as late as 43 minutes after the test injection of the antigen (corpuscles) presents, as in the acute shock in this species, a mechanical obstruction sufficient to account for the fatal termination.* This observation suggests the possibility that the cachexia of Arthus is due to a slightly less degree of such obstruction, which persists. Actually, in one instance of death of a sensitized rabbit occurring several weeks after the test injection (which had produced immediate severe symptoms from which the animal soon recovered), the pathological finding corresponded with the anticipated effects of a prolonged obstruction to the passage of blood through the pulmonary circulation.^(b) The lungs were of a dark red color and of markedly increased consistence, though not consolidated. The right ventricle of the heart was greatly dilated and filled with a mixed red and white postmortem blood clot. The wall of the right ventricle was thin, over a considerable area, to translucency, and the area of thinning was found, on microscopical examination, to be devoid of muscle elements. The cavity of the left ventricle was contracted. The chest and abdominal cavities were filled with a clear, straw-colored fluid. The animal, at death, presented a marked cachexia, having lost a large percentage of its weight since the test injection.

Protracted Anaphylactic Shock in the Dog.—The protracted shock was the first form of anaphylaxis to be studied in the dog, and when death resulted, after such a course, the pathological findings differed considerably from those of the acute shock studied by Weil. The intense degree of congestion of the liver that dominates the pathological picture in the acute shock is rarely if ever seen in the protracted form; the engorgement of the abdominal veins, on the other hand, is, in the latter form, the most prominent finding, this feature being much less marked, though present, in acute shock.

The intense engorgement of the abdominal veins was likened, by Pearce and Eisenbrey, to the similar condition noted in the surgical shock of human beings—a “bleeding into the individual’s own veins”—

* Unpublished observation of writer.

References: (a) 100. (b) 60.

and it was considered by these authors to be due to a local effect on those vessels. However, as Pearce and Eisenbrey noted a visible enlargement of the liver in the dogs that succumbed after more protracted shock, it would seem probable that here, also, the hepatic mechanism suggested by Weil is operative in the causation of the portal stasis. Accepting Weil's well-founded explanation, we can assume, further, that, in the protracted shock in the dog, the effect of the reaction on the liver has not caused a degree of blood absorption, by that organ, great enough to bring about the fatal issue by itself, death, in such a case, not supervening until the portal stasis has reached an intensity that compensates for the deficiency of congestion in the liver.

It is convenient, here, to refer to a possible difference between the mechanism of the anaphylaxis reaction in the dog and that in the guinea pig, which could be inferred from an experiment reported by Manwaring.

It has been found that the function of the mechanism through which the antibody-antigen reaction operates to produce the physiological effect of anaphylactic shock in the guinea pig (that is, the contractility of smooth muscle tissue) remains intact after recovery from such shock. This was early demonstrated by the observation that a guinea pig which has been sensitized simultaneously with two different antigens and has recovered from a severe shock upon the injection of one of these antigens, can immediately be fatally shocked by the injection of the other antigen. Moreover, that function is unaffected by the more gradual process of desensitization, since a sensitized guinea pig that has been completely desensitized by the suitable administration of the antigen can be, at once, resensitized.^(a)

Manwaring,^(b) in an experiment that has received little attention in the literature, showed that immediately after a passively sensitized dog has been shocked by the injection of the antigen it cannot be resensitized, even by the direct transfusion of a large quantity (500 c.c.) of blood from the same sensitized dog which had served as donor for the first passive sensitization. The possibility that the failure to become resensitized was due to the presence, in the blood of the experimental dog, of some of the previously injected antigen, was excluded by perfusing the animal with about 650 c.c. of normal dog's blood between the first injection of the antigen and the second perfusion with the sensitized dog's blood.

Manwaring concluded, from this experiment, that the reacting tissues of the dog, which he showed to be situated in the liver, are exhausted by the shock of anaphylaxis.

The question raised by this observation is similar to that presented by the relations that have been found to exist between peptone poisoning and anaphylactic shock in the dog.

Biedl and Kraus,^(c) who first noted the similarity of the symptoms of anaphylactic shock and of peptone poisoning in dogs—a fall of blood-pressure and a condition of incoagulability of the blood occurring in

both instances—found that the sensitized dog is refractory to the re-injection of the antigen if this is undertaken soon after the animal has recovered from an intoxicating dose of peptone. They reported, also, that a previously induced anaphylactic shock in the dog protects the animal somewhat against the effect of peptone injection.

These authors interpret their results as indicating that the shock of the anaphylaxis reaction is caused by the formation of toxic digestion products identical with those that are present in commercial peptone.

Weil,^(a) on the other hand, saw, in the mutually protective action of peptone poisoning and anaphylactic shock, merely the operation of the principle suggested by Manwaring in explanation of the failure of resensitization in desensitized dogs, namely, an exhaustion of the cellular mechanism (in the liver) in which the primary anaphylaxis reaction takes place.

The phenomena just discussed might be thought to be susceptible of another explanation.

The dog's liver, after the shock of peptone poisoning and of anaphylaxis, is probably more or less excluded from the blood circulation on account of the intense hepatic congestion, which is the chief pathological change in both of these conditions,^(b) the obstruction to the blood flow through the liver being indicated by the marked stasis in the portal tributaries. It is conceivable that this partial, temporary exclusion from the circulation of the demonstrated site of reaction, in anaphylaxis and peptone poisoning following either of these processes, might place the sensitive tissues out of immediate reach of the subsequently injected antigen or peptone, whereby a local resistance would be only simulated.

Against this explanation, however, stand the observations of Voegtlin and Berthelm^(c) and of Deneke,^(d) showing that the complete exclusion of the liver from the portal circulation in a sensitized dog by means of the Eck fistula does not prevent the subsequent production of anaphylactic shock by the injection of the antigen, the latter reaching the liver in sufficient amount through the hepatic artery.

Moreover, it is stated by Biedl and Kraus^(e) that the insensitiveness of sensitized dogs to the injection of the antigen after peptone "shock" persists for (at least) 24 hours, after which interval the blood-pressure has returned to normal.

The conclusion of Manwaring and of Weil seems therefore justified, namely, that, different from the sensitive tissues in the lungs of the guinea pig, those in the liver of the dog, after sustaining anaphylactic shock, lose, for a time, at least, their power of responding, in the typical manner, to the antigen-antibody reaction of anaphylaxis.

Summary of the Pathology of Anaphylactic Shock.—The wide differences that are apparent in the pathology of anaphylactic shock, in the three animal species in which that phenomenon has been chiefly studied, seem to depend on the *particular susceptibility of a certain tissue* or system of tissues, which is different in the three animals, to irritating influ-

ences. This is indicated by the fact that various toxic agents cause, in the different animals, the symptoms and pathological changes that are peculiar to anaphylactic shock in the respective animal. Thus fresh normal serum, for example, causes, in the guinea pig, anaphylactiform symptoms, the autopsy revealing the characteristic Auer-Lewis lung inflation without obstruction of the pulmonary circulation. In the rabbit, dead after the intravenous injection of normal serum, the lungs are collapsed, as in anaphylactic shock, but, in agreement with the pathology of that condition in the rabbit, the pulmonary circulation is impermeable.* The influence of the intravenous injection of normal serum on the dog is the same, with respect to the coagulability of the blood^(a) and to the blood-pressure, as that of antigen in the sensitized dog. Moreover, the passage of normal ox serum through the isolated normal dog's liver has been shown, by Nolf,^(a) to cause the secretion of anticoagulants by that organ as is the case when antigen is passed through the isolated liver of the sensitized dog.

It may be assumed, therefore, that at the reinjection in anaphylaxis, the meeting and interaction of antigen and antibody takes place in the same tissues in the different animals, but that such interaction in the tissues of the guinea pig, the rabbit and the dog produces, respectively, a physiological response only in the unstriated muscle of the bronchi, and other viscera, the vascular musculature and the tissues of the liver.

Anaphylaxis in Human Beings.—It has become the almost universal practice of writers in this field to designate as expressions of anaphylaxis the various clinical phenomena which will be considered under the subject of allergy—such phenomena as hay-fever, serum disease, food idiosyncrasy and even drug idiosyncrasy.

The idea that these phenomena are the result of antibody-antigen reactions originated in the theory of von Pirquet and Schick regarding serum allergy, which, in point of time, actually preceded the discovery of the antibody-antigen nature of the anaphylaxis reaction itself and which naturally was strengthened by that discovery. The demonstrated fact that the usual seasonal hay-fever, excited by pollens, the active principle of which was assumed to be antigenic proteins, appeared to warrant the belief that this condition, also, is the result of an antibody-antigen reaction. A similar explanation seemed plausible in the instances of food idiosyncrasy and those of susceptibility to poison-ivy. Finally, the similarity of the clinical manifestations of serum allergy and those of drug allergy was regarded, by some, as indicating the anaphylactic nature of the latter condition.

It will be shown in the consideration of the phenomenon of "serum disease" that not only is the theory of von Pirquet and Schick regarding that condition quite devoid of proof, but it appears, on account of many observations, an improbable explanation. Furthermore, the exciting agent of late hay-fever (isolated from the pollen of rag-weed)

* Unpublished observation of the writer.
Reference: (a) 174.

has been found to be lacking in antigenic property ^(a) and such property is also not possessed by the exciting agent of strawberries in the idiosyncrasy to that fruit. The difficulty offered to the anaphylaxis theory of drug idiosyncrasy by the fact that the drugs are not antigenic substances has not been overcome by the idea of Wolff-Eisner, which will be discussed in the chapter on drug allergy.

Tuberculin sensitiveness has been regarded by some as an expression of anaphylaxis, as have, also, the phenomena of eclampsia and sympathetic ophthalmia and the symptoms of infectious diseases. For all of these assumptions proof is still lacking, the experimental evidence bearing on them being inconclusive or highly questionable as to its application.

The typical phenomenon of anaphylaxis, in the three experimental animals that have been most used in the study of that condition, consists in the almost immediate onset of symptoms, which quickly end in death, *following a second administration* of the antigen and, as has already been pointed out, the amount of serum that is required to kill a sensitized guinea pig is much greater by the subcutaneous route than it is by intravenous injection. There is no record of a sensitized rabbit or dog having been killed by subcutaneous injection of the antigen, although such animals have, on innumerable occasions, received ordinary injections (2-5 c.c.) of the antigen by that route.

A review of the reported instances of almost immediate symptoms, ending in death in human individuals following serum injections, reveals the important fact that the circumstances of those occurrences were the reverse of those, just mentioned, under which anaphylactic shock takes place. In most of the cases the injection was a primary one and a relatively small one, given by the subcutaneous route. In one instance reported by McKeen,^(b) the amount injected (500 units—probably not more than 0.5 c.c.) corresponds with about 0.0025 c.c. for a 250-gram guinea pig, an amount of serum that is far less than that required to produce symptoms in a sensitized guinea pig by subcutaneous administration. It is, thus, entirely unjustified to consider these cases as representing anaphylactic shock in human beings.

There are reported instances of severe general symptoms following a *reinjection* of serum into human beings,^(c) the primary injection having produced no symptoms. Such cases simulate the anaphylaxis experiment, and the possibility that they actually represent anaphylactic shock cannot be at once rejected. It may be noted, however, that death occurred in only few such cases, the fatal injection being given, in one instance, by the *subcutaneous* route,^(d) in three others ^(e) intradurally (30 c.c.) in the course of cerebrospinal meningitis, in one case ^(f) intravenously in a case of pseudoleukemia complicated with diphtheria, and in another case ^(g) by the intravenous route after a short interval following the primary (intramuscular) injection.

The number of instances in which the intravenous reinjection of

References: (a) 61. (b) 158. (c) 86, 222, 52, 142, 157, 114. (d) 122. (e) 105. (f) 86. (g) 105.

serum disease and of the food idiosyncrasies have their counterpart, both as to the character of the lesions and as to the factor of time-interval in their development, in the specific idiosyncrasies to the non-antigenic drugs and chemical substances. These latter phenomena are certainly not due to antigen-antibody reactions.

The list of the phenomena of local anaphylaxis is, thus, limited to the possible single example of the local hypersensitiveness of Arthus in the rabbit. All of the specific local reactions in human beings are to be considered under the head of Allergy.

ANTIANAPHYLAXIS

Animals that have been actively or passively sensitized may, by various means, be made relatively more or less resistant to the usual test injection of anaphylaxis. Such resistance is quantitatively or qualitatively different according to the manner and means of its production; the differences shown are due to differences in the underlying mechanism and in this respect it is necessary to distinguish *non-specific* and *specific* forms of the phenomenon. The need of a term to apply to all forms of the phenomenon of resistance to, or interference with, the injurious effects of "reinjection" is met with the familiar designation "antianaphylaxis," which was invented by Besredka.

Non-specific Antianaphylaxis.—The fact has already been mentioned that if all of a group of guinea pigs of nearly equal weight are sensitized, either actively or passively, with quantitatively the same preliminary injection, it will be found that the minimal lethal dose of the anaphylactogen will be very nearly the same for all of these animals. If, however, a short time previous to the test injection, some of the group of sensitized guinea pigs receive an injection of some material other than the corresponding anaphylactogen, such as inorganic salts, peptone, foreign serum or other proteid substances, such individuals may not then succumb to the injection of the minimal lethal quantity of the anaphylactogen as determined for the other members of the group.

Such non-specific interference—antianaphylaxis—is not absolute; that is, anaphylactic shock in full measure can be elicited in such resistant animals merely by the administration of a multiple of the determined minimal lethal dose of the antigen. The mechanism of non-specific antianaphylaxis is not understood. It has been a pitfall in the way of some investigators of anaphylaxis, but it possesses, at present, no other importance.

Specific Antianaphylaxis.—Two forms of specific antianaphylaxis are distinguishable both as to the manner of production and as to the mechanism of the interference. One of these forms has been designated with the term desensitization; the other form may be referred to as antianaphylaxis by antibody protection.

DESENSITIZATION.—If a guinea pig that has been actively or passively sensitized be given, by subcutaneous injection, a suitable quantity of the respective anaphylactogen, the animal will be found, after an in-

interval of several hours, to have lost completely its previous hypersensitiveness, so that now its immediate behavior toward injections of the anaphylactogen is in all respects the same as that of a normal guinea pig.

The difference between this state and that of non-specific antianaphylaxis is clear and it points to a difference in the mechanism of the two phenomena. This specific form of antianaphylaxis has been shown to be due solely to a specific neutralization of the antibodies situated in the sensitive tissues. This is demonstrated by the fact that after a sensitized guinea pig has been rendered specifically quite insensitive it can at once be passively resensitized with nearly the same minimal quantity of immune serum that is required for the passive sensitization of a normal animal.

The mechanism of this form of antianaphylaxis is best designated with the term desensitization, which signifies a complete removal of the previous state of hypersensitiveness.

The specificity of desensitization may be demonstrated, in guinea pigs that have been sensitized against more than one anaphylactogen, by desensitizing the animal to one of the anaphylactogens. The animal thus treated will be found to be still hypersensitive to the other anaphylactogens, though in a slightly lesser degree (non-specific interference), as shown by a somewhat increased minimal lethal dose of the other anaphylactogens.

Desensitization can be accomplished not only by subcutaneous injection but also through the peritoneal or venous routes. It was early noted that animals which had recovered from anaphylactic shock following intravenous injections were insensitive to subsequent intraperitoneal injection of the usual intoxicating doses of the antigen. Later it was found that, by the slow injection of the dilute antigen, complete desensitization can be attained through the venous route without the production of anaphylactic shock.

The obvious explanation of the absence of symptoms during the process of desensitization has been recognized in the slowness with which the antibodies are saturated, the cause of the shock of anaphylaxis being seen, conversely, in the sudden meeting of a completely or nearly completely neutralizing amount of antigen with the antibody in the sensitive tissues.

Mention has just been made of the insensitiveness of guinea pigs that have recovered from anaphylactic shock after intravenous injection of nearly lethal amounts of the antigen. Such resistance was found to be generally not complete though differing from the non-specific antianaphylaxis in that the former is exerted against greater amounts of the antigen (5-10 lethal doses) than is the latter ($1\frac{1}{2}$ -2 lethal doses). This "partial desensitization" was quantitatively analyzed by Weil ^(a) in both active and passive anaphylaxis and with the latter technic the following characteristic phenomenon was observed: guinea pigs that had been passively sensitized with the minimal sensitizing amount of rabbit's antiserum were regularly killed with the minimal quantity of

0.05 c.c. of the antigen (horse serum). The minimal lethal dose of the antigen for animals that had been sensitized with two to six minimal sensitizing amounts of the antiserum was found to be 0.003–0.005 c.c.; but when such sensitized animals were partially desensitized with a subcutaneous injection of 0.01 c.c. of the antigen the minimal lethal dose of the latter was increased in all cases (that is, in the animals sensitized with 2 or 4 or 6 minimal sensitizing amounts of antiserum) to 0.5 c.c. Moreover, in animals sensitized with six sensitizing amounts of the antiserum the minimal lethal dose of the antigen was increased in the same degree, whether the partial desensitization was carried out with the injection of 0.01 c.c. or 0.02 c.c. or 0.05 c.c. of the antigen.

Two peculiarities are obvious in these results: one is presented by the constant increase of the minimal lethal dose of the antigen after widely various quantitative combinations of sensitizing antiserum and partially desensitizing antigen. The other peculiarity lies in the fact that after the least sensitizing injection of the antiserum, the minimal lethal dose of the antigen was only one-tenth as great as that required to kill any of the partially desensitized animals.

Since these results show that "antigen does not depress the reactivity of cellular antibody in regular quantitative ratios," Weil believed that the living cell so modifies the antibody that its property of combining with antigen is changed from the "quantitative one" of the test-tube reaction to a different one, which he set in analogy with that exhibited in the Danysz-Dungern phenomenon. According to Weil the precipitin reaction in the test-tube takes place according to chemical proportions, whereas the union of cellular antibody with antigen occurs according to the physical proportions of colloidal reactions.

This explanation, which is based on purely quantitative considerations, throws no light on the difficulty presented in the second "peculiarity" referred to above. This peculiarity is not susceptible of an interpretation based on quantitative considerations alone, because if the unsaturated residue of the cellular antibody possessed the same qualitative reactivity as all of that already neutralized, it would react with a quantity of antigen no greater than that required for animals sensitized with the minimal sensitizing amount of the antiserum.

This discrepancy could, however, be due to the known existence, in the sensitizing antiserum, of antibodies of different qualitative reactivity, that is, of different avidity. It may be assumed that the partially desensitizing injections have the effect of neutralizing only or chiefly the antibodies of the greater avidity. In this case the corresponding test-tube experiment should give the same results.

SPECIFIC ANTIANAPHYLAXIS BY ANTIBODY PROTECTION.—It was early observed that if guinea pigs which had received an actively sensitizing injection of antigen were injected a second time, shortly before the establishment of the expected hypersensitiveness, with the same material, they did not become susceptible to the usual test injection until after a much longer period than after a single injection. This form of anti-anaphylaxis was particularly puzzling on account of the fact that the

blood of such resistant animals contained demonstrable antibodies in greater amount than that of ordinarily sensitized animals.

The first explanation of this resistance was contributed by Weil,^(a) who demonstrated, first, that the resistance is not absolute, since it can be overcome with relatively large intravenous injections of the antigen and secondly, that it can be imitated by injecting heterologous or homologous antiserum into ordinarily sensitized animals previous to the test injection.

The resistance of the "immune" guinea pig was, thus, referred by Weil to the antibodies present in the blood, the injected antigen being prevented from reaching the sensitive cells by its reaction with the circulating antibodies.

The protective influence of circulating antibodies was shown by Weil to be operative, also, in the process of desensitization.^(b) Weil found that if small but ordinarily desensitizing quantities of antigen are injected subcutaneously into passively sensitized guinea pigs that had been given large protective injections of antiserum, the circulating antibodies are found to be entirely "neutralized," although the uterine muscle still remains sensitive. The antigen, slowly absorbed from its subcutaneous site, had been intercepted by the antibodies in the blood.

Weil's conclusions have been confirmed and amplified by Manwaring and Kusama,^(c) who found that the isolated tissues (bronchial musculature) of the immune guinea pig are, actually, more sensitive to contact with the antigen than are those of the ordinarily sensitized animal.

Because of the fact, observed by Weil, that, notwithstanding a considerable quantitative resistance offered to the injection of antigen by guinea pigs that had received large preparatory injections of the antigen (two cubic centimeters on each of three successive days), the blood of such animals contained no correspondingly great amount of antibodies. Weil saw the necessity of seeking some cause for that resistance other and, as he came to believe, more important than the protective action of circulating antibodies. That cause he assumed to be antigen persisting in the cells and depressing the activity of the coexistent antibody. Some support of this explanation was found in Weil's observation that a similar but actually much greater quantitative resistance could be produced in passively sensitized guinea pigs by means of partial desensitization, that is, by the injection of sublethal quantities of antigen.

In order to demonstrate the coexistence of antigen and antibody in the cells, Weil passively sensitized guinea pigs with antihorse immune serum of the rabbit and after a certain interval he was able, with the anaphylaxis reaction, to show the presence, in the uterine muscle, of both the injected antihorse antibodies of the rabbit and antirabbit antibodies, which had been developed by the guinea pig itself. Weil, thus, looked upon the persisting antihorse antibodies as "antigen." However, there is no evidence in the experiments of Weil that these

antibodies have a specific relation to the anti-rabbit antibodies that could be shown to coexist with them. Such a relationship would have to be clearly proven in order to establish the hypothesis advocated by Weil, because the presence of unrelated antigen is known not to cause such resistance in anaphylaxis as that observed by Weil in his "immune" or partially desensitized animals.

That the hypothetical factor of persisting intracellular antigen cannot explain all instances of resistance in "immune" guinea pigs, seems clear from the observation of Manwaring and Kusama, referred to above, that the isolated sensitive tissue of "immune" guinea pigs is actually more susceptible to contact with the antigen than is that of the ordinarily sensitized animal.

ANTISENSITIZATION

Richard Weil, in the course of several publications,^(a) described instances of a resistance to passive sensitization in guinea pigs that had received injections of normal rabbit's serum. This phenomenon was later subjected to extensive experimental study, by Weil, who coined for it the designation "antisensitization."^(b) The results of Weil's investigations of the phenomenon are as follows:

(1) The previous injection of rabbit's serum obstructs the passive sensitization with rabbit's immune serum but not with a homologous (guinea pig's) immune serum.

(2) The interference is established after an incubation period, which is longer (8 days) after small injections (0.1 to 0.5 c.c. repeated) than after large injections (1 to 8 c.c.), that is, 4 days.

(3) The duration of the normal period of heterologous passive sensitization in guinea pigs is 6 days. If the guinea pigs have received 0.1 c.c. of normal rabbit's serum 2 to 8 days previously, the period of passive sensitization with heterologous serum is shortened to barely 5 days. This period may be shortened, also, by the injection of 0.6 c.c. of normal rabbit's serum made on the day following the passively sensitizing injection.

(4) The refractory condition of "antisensitization" persists for at least 68 days.

(5) Active sensitization is unaffected by the injection of large amounts of normal rabbit's serum.

The conclusion drawn by Weil from the foregoing observations: namely, that the phenomenon of "antisensitization" is due to the action of anti-antibodies, was strongly supported by the further demonstration by that investigator of a similarly obstructive action on the part of the serum of guinea pigs that had been highly immunized with rabbit's serum.

One difficulty in the theory offered by Weil to explain the phenomenon of "antisensitization" was encountered by him in the ob-

ervation that previous injection of sheep's serum, dog's serum or human serum also produced that condition. It was, therefore, apparently not specific. This difficulty was met by Weil with the demonstration that guinea pigs sensitized to rabbit's serum are actually hypersensitive to large injections of the three apparently unrelated sera. The "crossed" sensitization thus induced, indicated the existence of common antigenic substances in all of the four sera, and from this result Weil assumed that the "antisensitization" produced by the injection of "unrelated" sera was due to the neutralization of the sensitizing antibodies by the "group antibodies" developed against the common antigens in those sera.

This experimentally supported assumption conflicts with the observations of Ehrlich and Sachs^(a) on the action of anti-amboceptor (anti-antibody), which they found to be strictly specific.

However, the latter authors made use of complement as the indicator of the action of the anti-amboceptor, whereas Weil's indicator was the direct one of the sensitizing effect of the antihorse antibody. In other words the results obtained with the two methods need not be comparable.

THEORIES OF THE MECHANISM OF ANAPHYLACTIC SHOCK

The theories concerning the anaphylactic reaction that were proposed previous to the demonstration of its antibody-antigen nature by Friedmann^(b) and Otto^(c) possess only a historical interest, having contributed little to the development of the present views upon this question. For this reason the discussion of those theories will be omitted here.

The views of the present day upon the underlying mechanism of anaphylactic shock diverge both as to the *site* of the antibody-antigen reaction that causes the symptoms and as to *how* that reaction produces the shock.

The *site* of the antibody-antigen reaction of anaphylaxis is thought to be either the fluids of the body (humoral theories) or certain of the fixed tissues (cellular theories). While most of the authors commit themselves exclusively to one or the other of these two theories as to the site of the anaphylactic reaction, some combine the two theories in the belief that certain of the symptoms of anaphylaxis, especially those of acute shock, may be due to a cellular reaction, whereas other manifestations of the condition (those of delayed shock) are the result of a humoral reaction. As to *how* the antibody-antigen reaction of anaphylaxis produces the characteristic symptoms of that condition, there are two general divisions of opinion. One of these assumes a chemical change in one of the reacting elements (antigen or antibody) or in the medium in which the reaction takes place, such change resulting in the formation of a poisonous substance, which causes the symptoms of anaphylaxis. The other group of opinion assumes changes

of a physical nature in the medium in which the antibody-antigen reaction occurs, the latter being itself considered to be merely a phase alteration in which changes in chemical constitution are not involved.

Inasmuch as both the physical and the chemical explanations have been adopted by the different authors in both humoral and cellular theories of anaphylaxis, it is not practicable to discuss the various theories categorically.

Humoral Theories.—One of the earliest conceptions of the cause of anaphylactic shock assumed the production of a poison, which, at first, was supposed to be derived from the antigenic material by a process of digestion. This idea has been subjected to numerous variations.

The antigenic material, the antibody, and the normal constituents of the blood have been looked upon as the mother substance from which the poisonous digestion product is derived. The digestive process has been supposed to be accomplished by complement coöperating with antibody, by specific ferments that have been generated under the antigenic stimulus and finally by the normal ferments of the blood.

The main theory that anaphylactic shock is due to the formation of a poisonous digestion product is lacking in direct experimental evidence, since it is not yet shown that such products arise in anaphylactic shock and since the only motive of such a theory is found in the observation, in the blood of animals in anaphylactic shock, of a relatively late increase of non-proteid nitrogen, which, however, has not been shown to represent toxic digestion products, together with test-tube procedures that result in the formation of substances which are capable of producing anaphylactiform symptoms. The lack of force in this latter motive is clearly stated by Auer,^(a) who points out that the closest similarity of physiological effect is not proof of the identity of two agents.

The conception of Vaughan has been referred to in the discussion of antigenic specificity. It assumes the development of specific proteolytic ferments in response to the first injection, these supposedly differing from the normal ferments of the blood in their more rapid action and their specificity.

The conception of Richet^(b) is similar to the foregoing, being drawn, without further experimental evidence, merely from the symptomatology of anaphylactic shock in dogs. Richet assumes the formation, in the sensitized animal, of a substance, which he names "toxogenin," that is capable of splitting the antigen, at the second injection, "as emulsin splits amygdalin," into products, some of which are toxic.

The inadequacy of the experimental basis of the conception of Vaughan has already been pointed out. There are, furthermore, certain difficulties in the way of the theory as such. The studies concerning the ferments that arise as the result of the injection of foreign protein show these to be non-specific;^(c) moreover, the alleged demonstration of the once widely credited organ-specificity of the so-called "Abwehrfermente" of Abderhalden^(d) has proved to be fallacious.

Ferments have been observed to appear, also, after the injection of

References: (a) 20. (b) 198. (c) 1, 2, 3, 6, 113, 196. (d) 5.

non-antigenic substances (peptone) or of serum from animals of a related race,^(a) although serum does not give rise to the condition of anaphylaxis when injected into animals of a related race. Unlike the antibodies that carry the function of sensitization, the ferments arising from these procedures are thermolabile and they have been shown to be quite distinct from the precipitating and agglutinating antibodies.^(b) They appear in the blood of injected animals before the condition of hypersensitiveness is established and they disappear while that condition still exists in full force.^(c)

Vaughan believes that the "specific proteolytic ferments stored up in the cells of the animal as a result of the first treatment with the proteid remain in the cells as a zymogen until activated by the second injection of the same proteid."^(d) Such a theory leaves quite unexplained the passive transfer of the sensitization.

The lack of relationship between the phenomenon of anaphylactic shock and the proteolytic ferments that appear in the blood after injections of foreign protein is clearly apparent in the results of the study by Pearce and Williams.^(e) Of the important findings of that study may be mentioned that proteolytic enzymes could not be demonstrated in the blood of sensitized dogs previous to the test injection, though such ferments were found $\frac{1}{2}$ to $1\frac{1}{2}$ hours after the shock produced by that injection.

Independently of Vaughan, de Waele^(f) and later Biedl and Kraus^(g) and others, observing that anaphylactiform symptoms and pathological changes (acute death, inflation of the lungs in guinea pigs, vomiting and diarrhea, incoagulability of the blood and fall of blood-pressure in dogs) are produced by the injection of Witte peptone, reached the conclusion that anaphylactic shock is caused by the formation of toxic digestion products.

Aside from the fact that guinea pigs, which are so much more sensitive to the anaphylaxis reaction than dogs, are so much (100 times^(h)) less sensitive than dogs to injections of peptone, the view of de Waele does not explain why the amount of peptone required to kill guinea pigs is about 5000 times as great as the smallest lethal amount of protein for the passively sensitized animals.*

A similar wide discrepancy in the quantitative relationships in the dog has been pointed out by Weil⁽ⁱ⁾ in the results of Jobling,^(j) who found, in the blood of dogs in anaphylactic shock, an increase of non-coagulable nitrogen corresponding to about 35 mg. of peptone to 100 c.c. of serum. This amount of peptone is less than one-fortieth of the quantity necessary to kill a dog of corresponding weight.

More direct evidence of the formation of poisonous reaction products in anaphylactic shock was sought by mixing antigen and antibody with or without the addition of normal, complement-bearing serum and in-

* Weil found that 0.00005 gram of crystalline egg-albumen killed guinea pigs sensitized with 0.2 c.c. of antiserum; 0.25 gram of peptone is required to kill a guinea pig of the same weight by intravenous injection.

References: (a) 4. (b) 13. (c) 6, 13. (d) 230, see also 229. (e) 191. (f) 72. (g) 38. (h) 183. (i) 260. (j) 124, 125.

jecting the mixtures, after incubation, into normal animals. Many of the investigators who approached the problem of anaphylaxis in this way, did so with no preconception as to the nature of the process of the poison formation, but their work may be conveniently considered with that of those who conceived that process to be a fermentative one.

The earlier experiments with mixtures of antigen and antiserum were not satisfactory, inasmuch as the toxic action was not intense enough to produce the typical fatal shock of anaphylaxis in guinea pigs. Doerr and Russ,^(a) at last, succeeded, with extended incubation, in securing a fatal toxicity of the mixtures and a typical pathology of anaphylaxis in the injected guinea pigs.

Following Friedemann,^(b) who observed the development of anaphylactiform toxicity in complement-bearing rabbit's serum during its contact with specifically sensitized ox-blood corpuscles before the latter had begun to be hemolyzed, Friedberger* has contributed a large volume of experimental work on the thesis that the hypothetical poison of anaphylactic shock is derived from the anaphylactogen after its union with the antibody through a ferment action on the part of complement. The poisonous digestion product is designated by Friedberger as "anaphylatoxin."

Aside from its incompatibility with the established fact of the latent period of passive sensitization in the guinea pig and the entire absence of a demonstrated ferment property on the part of complement, this theory has been rendered untenable by the following considerations:

(1) Typical anaphylactic shock has been produced in animals whose blood had previously been completely deprived of its complementary function,^(c) and, furthermore, an anaphylactiform toxicity has been demonstrated in incubated antigen-antiserum mixtures in the complete absence of complement.^(d) This latter observation is not susceptible of the explanation that the toxic property of the mixtures is developed, after their injection, by the rapid action of the complement in the blood of the injected animal, because of the fact that such mixtures become toxic only after prolonged incubation.

(2) Anaphylactiform toxicity has been demonstrated in mixtures of complement-bearing serum with kaolin or barium sulphate, which had been treated with immune serum alone^(e) or with inactivated normal serum,^(f) that is, in the absence of antigen, in the first instance, and in the absence of both antigen and antibody in the latter.

(3) "Anaphylatoxin" has been demonstrated in fresh normal guinea pig's serum that had been kept in contact with merely a Berkefeld filter^(g) or with agar^(h) or starch⁽ⁱ⁾ combinations that appear far removed from those which give rise to anaphylactic shock. Friedberger's explanation of the formation of anaphylatoxin in mixtures of agar and guinea pig's serum as due to a combination of normal amboceptors in the serum, with a trace of nitrogenous and therefore antigenic substance

* See index of *Ztschr. f. Immunit.* for the years 1909 to 1912.

References: (a) 76. (b) 103. (c) 151. (d) 84. (e) 130. (f) 201. (g) 76, p. 1050. (h) 44. (i) 167.

(which has been demonstrated in the agar) followed by a "digestion" of that substance with complement, has been refuted on quantitative grounds by Doerr,^(a) who points out that the entire weight of the nitrogenous material in agar, if taken in the most toxic known protein derivative—histamin, is insufficient to cause symptoms in guinea pigs.

As Dale^(b) says, it can be plausibly argued that the hypothetical digestion process, which is supposed to be the cause of the symptoms of anaphylactic shock, may occur within the cells, and that under this circumstance the amount of the resulting toxic product need not be large enough to be detected with the methods at our disposal. In this form the hypothesis is placed outside the range of experimental examination except for the important observation of Dale that the curve of the specific reaction of sensitized uterine muscle to the antigen is identical, in every respect, with that produced by the action of the ready-formed proteid poison histamin. *This observation must stand as an obstacle to the acceptance of even the cellular variety of the digestion theory of anaphylactic shock, since the ferment action in anaphylactic shock would have to be assumed to take place in a manner contrary to that of any known ferment, that is, with a total lack of incubation period.*

The form of the digestion theory set forth by Jobling,^(c) Petersen and Eggstein, according to which there is, during the latent period of active sensitization, a progressively increasing power of instantaneous "mobilization" of normally existing ferments at the reinjection, which attack the normal blood proteins—chiefly the proteoses—appears not to account for the phenomenon of the latent period in passive sensitization. The same difficulty stands in the way of Bronfenbrenner's^(d) idea that the normal ferments of the blood are left free to attack the normal blood proteins by the mere withdrawal of the normally restraining influence of the antiferment—"antitrypsin"—which was found, by Jobling, Petersen and Eggstein, to be diminished in anaphylactic shock.

In a recent series of studies^(e) with de Kruif, F. O. Novy, R. L. Novy and German, F. G. Novy, disregarding Auer's protest, frankly adopts the criterion of physiological action as satisfactory indication of the identity of toxic processes. On the basis of this criterion these authors assume the production of "anaphylatoxin" in explanation of the toxicity of precoagulation blood, of normal sera, of agar and of peptone, as well as in explanation of anaphylactic shock in all species of animals. According to Novy and his co-workers, "it may be assumed that a poison, in the sense of a chemical entity rather than as a property of a dispersed state, is produced in the reaction which follows the administration of the second dose."^(f) "The results contra-indicate the theories of absorption and of proteolysis." "The specific anaphylactic shock is the result of anaphylatoxin production, *in corpore*, consequent upon the inducing action of a body which is formed by the union, or otherwise, of antigen and its specific antibody."^(g) The mechanism of the poison production is thus left by the authors, without analogy in chemistry—

References: (a) 77, p. 345. (b) 66. (c) 124. (d) 47. (e) 69, 70, 176, 177, 178, 179, 180, 181, 182, 183, 184. (f) 181, p. 793. (g) 181, p. 832.

Cellular Theory.—The idea that the antibody-antigen reaction that causes the shock of anaphylaxis takes place in or upon the cells of the fixed tissues originated with Besredka,^(a) who believes that the reaction which determines the shock occurs in certain cells of the central nervous system. It may be remarked, here, that since, in the guinea pig, the rabbit and the dog, the pathological changes of anaphylaxis have been shown to occur independently of the central nervous system, the latter phase of Besredka's theory, which this author still maintains,^(b) is evidently untenable.

The theory of a cellular site of reaction in anaphylaxis, which, at first, was adopted by Friedberger^(c) and others, was brought into harmony with the generally accepted hypothesis of Ehrlich regarding antibody production, the shock-producing reaction in active anaphylaxis being assumed to take place between the reinjected antigen and the "sessile" receptors that have not yet been thrown off by the cells that produced them. The cellular theory, however, does not depend on the survival of the Ehrlich hypothesis, since the refutation of that hypothesis could not disturb the well-founded fact that antibody production is a function of body cells.

In the brief period of its first general acceptance, the cellular theory was adapted, on theoretical grounds, to the various phenomena of anaphylaxis and particularly to those of the latent period of passive sensitization and to the resistance of "immunized" guinea pigs; that is, guinea pigs which have received more than one injection of the antigen (antianaphylaxis by antibody protection). It was the failure of Friedberger^(d) to demonstrate the mechanism of the latter phenomenon, in accordance with the cellular theory, by the injection of immune serum into sensitized guinea pigs that forced this investigator to abandon the cellular theory and to inaugurate the long series of studies which contributed so much to the development and general acceptance of the humoral theories.

The humoral theory had hardly gotten under way when, from two independent sources, experimental evidence was recorded that pointed to its inadequacy. Schultz^(e) excised the involuntary muscle of various organs (intestine, uterus, bladder, aorta and vena cava) of normal and actively sensitized guinea pigs and showed that the tissues of the latter animals were more sensitive to direct contact with the antigen than were those of the former. These experiments suggested that the state of anaphylactic hypersensitiveness lay in the muscle tissues themselves and was not a property of the blood, as held by the humoralists. However, since the vessels of the excised muscle still contain some blood, the experiments could not be accepted as conclusive. Moreover, the differences observed by Schultz between the reactions of the normal and the sensitized tissues were so moderate that that author was led to consider the anaphylactic reaction to be only an exaggeration of the normal effect of the same material.

Manwaring^(f) approached the problem from a technically opposite

References: (a) 33, 37. (b) 35. (c) 95. (d) 97. (e) 214. (f) 155.

standpoint, though with the same end in view, that of testing the sensitiveness of the tissues after the exclusion of the influence of the circulating antibodies. Manwaring replaced the greater part of the blood of a sensitized dog with the transfused blood of a much larger normal dog and found that the former remained hypersensitive to the antigen.

The experiments of Schultz were confirmed and extended by Dale, Weil and others. Dale,^(a) using exclusively the uterine muscle of young virgin guinea pigs, made the isolation of the muscle more nearly complete by a prolonged perfusion, through the abdominal aorta, with Ringer's solution. The results obtained by Dale revealed the same wide difference in the response of normal and sensitized muscle tissue as are seen after the injection of the antigen into normal and anaphylactic animals.

The displacement experiments of Manwaring were confirmed by Pearce and Eisenbrey^(b) and others,^(c) and the technic was applied to passively sensitized guinea pigs under circumstances in which the circulating blood of the sensitized animal must have contained less than a single minimal sensitizing amount of antibodies, even before the transfusion was begun,^(c) under these circumstances, also, the sensitization was maintained in full force.

The latent period of passive sensitization in the guinea pig has been referred to as an unsurmounted obstacle to the formulation of any humoral theory of anaphylaxis. The conditions existing in that period are serviceable in refutation of the objection on the part of the humoralists to the interpretation placed, by the adherents of the cellular theory, on the results of the various perfusion experiments, notably those of Dale on the isolated uterine muscle. The objection was that no assurance could be given that the perfusion of the uterus, as carried out by Dale, actually resulted in the removal from the organ of all of the blood and other fluid-containing antibodies. This objection derives further weight from the experiments of Larson and Bell,^(d) who have demonstrated the incompleteness of the displacement of blood by the process of perfusion.

However, as has been intimated, the conditions prevailing during the latent period of passive sensitization in the guinea pig are, in themselves, proof of the groundlessness of the objection referred to; because test injections undertaken during that period have shown that no amount of antibodies in the circulating fluid alone can mediate the reaction of anaphylactic shock.

Moreover, Weil,^(e) by demonstrating the insensitiveness of the uterine muscle of the guinea pig when that tissue was tested during the latent period of passive sensitization (that is, when the residue of blood in the isolated uterus was known to contain abundant antibodies, which, however, had not yet formed an effective combination with the cells of the organ), thus, completed the refutation of the objection.

The foregoing group of experiments seemed to make the conclusion

inevitable that *the antibody-antigen reaction of anaphylaxis occurs in or upon the fixed cells of the susceptible tissue, the latter being different in the different animal species.* This conclusion was, finally, established by Weil's demonstration of the *protective influence of circulating antibodies,*^(a) which is incompatible with any humoral theory of anaphylaxis.

The cellular theory of anaphylaxis is, thus, forced upon our acceptance by facts that admit of no other interpretation. In the light of that theory, moreover, all of the principal phenomena of anaphylaxis become intelligible and there is no phenomenon of anaphylaxis which is necessarily at variance with that theory.

A cellular site of the antibody-antigen reaction must be assumed in anaphylactic shock in all of the three animals in which that phenomenon has been chiefly studied. In the guinea pig, beside the isolation experiments of Dale and Weil and the displacement experiments of the writer and of Fenyvessy and Freund, the latent period of passive sensitization demand the assumption of a cellular site of reaction. In the rabbit Doerr and Pick^(b) observed fatal anaphylactic shock upon reinjecting the animal at a time when the previously existing circulating antibodies had disappeared from the blood. The writer has supplemented this observation with a perfusion experiment on the isolated lung of the sensitized rabbit similar to that of Dale on the uterus of the sensitized guinea pig. After the pulmonary circulation had been washed for five minutes with warm physiological saline solution, the antigen (egg-white) was injected through the wall of the rubber tubing through which the perfusion fluid was being conducted to the pulmonary artery. Within one minute after the antigen had reached the lungs the pulmonary circulation became completely impermeable to a pressure considerably greater than the normal blood-pressure in the pulmonary artery. In the dog the displacement experiments of Manwaring and of Pearce and Eisenbrey, as well as the isolation experiments of Manwaring, of Voegtlin and Bernheim and of Deneke, together with the demonstration, by Weil, that the blood of dogs dead in acute anaphylactic shock is not toxic, can be explained only by the assumption of a cellular reaction site.

The idea of some authors that the site of reaction in anaphylaxis, if not chiefly humoral in the acute form of shock, is so, at least, in the delayed or protracted form, has little support in the established facts of the pathology of anaphylaxis in the three chief experimental animals. In both the dog and the rabbit, as we have seen, the pathology of the acute shock and of the protracted shock seems clearly the result of an identical mechanism in the respective animal. In the guinea pig, while the pathology in protracted shock is not so patent as it is in the acute shock, nevertheless, the observations of Auer, to which reference has been made,* warn against the assumption of a difference in principle in the underlying mechanism of these two forms of anaphylactic shock in the guinea pig.

* See page 130.

References: (a) 249, 253. (b) Cited by Doerr, 76.

Furthermore, the assumption of a humoral site of reaction in the delayed shock of anaphylaxis in the guinea pig has been shown, by Weil, to be untenable. Weil^(a) found, *first*, that the delayed form of anaphylactic shock can be elicited by intraperitoneal injection of the antigen into guinea pigs in whose blood no sensitizing antibodies can be demonstrated, this observation thus proving that the participation of circulating antibodies is not essential in the production of delayed shock; *secondly*, that a reaction corresponding with that of delayed shock can be produced in the isolated uterine muscle of the sensitized guinea pig by the gradual addition of antigen to the bath in which the uterus was suspended; *thirdly*, that during the latent period of passive sensitization, although antibodies are present in the circulating fluids, delayed shock cannot be elicited.

The comparative observations of Dale^(b) on the effect of histamin and that of the anaphylaxis reaction on the isolated uterine muscle of the guinea pig have rendered improbable a ferment nature of the reaction that takes place in the sensitive tissues in anaphylaxis. Hence, Dale has formulated a physical conception of that reaction, which, for the present, must remain purely hypothetical. Dale says, in substance:

"The effect can probably be accounted for by the mere initiation of those changes in the state of aggregation of the colloidal particles, which, when antibody and antigen are present in appropriate proportions and sufficient time is allowed, result in the formation of a visible precipitate. It is not, however, necessary to assume an identity of precipitin and anaphylaxis antibody. If they be identical, as seems very probable, it is not necessary that the antibody be present in such proportion as to give, with antigen, a visible precipitate. All that is needed is that the antibody should have such a specific physical relation to the antigen that when the two meet, a disturbance of the condition of colloidal solution is set up in the muscle fiber."

Physical Theory.—There is still to be considered the physical theory of Nolf,^(c) who conceives the anaphylaxis reaction as occurring in the circulating fluid and as producing, there, a disturbance of the delicately adjusted "colloidal balance," whereby a deposit of fibrin on the leukocytes and vascular endothelium is brought about. In view of the hypothetical nature of this fundamental assumption of Nolf, a discussion of the application of the theory to the explanation of the various phenomena of anaphylaxis may be dispensed with here.

The inadequacy of the theory of Nolf is evident merely from the fact that it presupposes a humoral site of reaction in anaphylaxis. In fact, its application to the explanation of anaphylactic shock, particularly in dogs, with which animal Nolf's observations were chiefly made, seems precluded by Deneke's observation that the exclusion of the liver from the portal circulation of the dog, while it does not interfere with the production of antibodies, yet prevents the establishment of active sensitization in that animal.

If, as Nolf assumes, the liver does not participate in the antibody-antigen reaction of anaphylaxis, but is secondarily involved, it is quite incomprehensible why, under the conditions of Deneke's procedure, the reinjection does not cause anaphylactic shock, especially as the exclusion of the liver from the portal circulation in an already sensitized dog does not prevent the subsequent production of shock on a reinjection of the antigen.

ALLERGY

Definition.—Allergy * is a condition of hypersensitiveness in which an antibody-antigen reaction has not been shown to be the underlying cause of the symptoms that characterize it.

It will be convenient to designate the exciting agents as allergy with the term "Allergen," ** which was invented by von Pirquet.

General Allergic Symptoms.—The phenomena of specific hypersensitiveness that must be associated, in accordance with the proposed definition of allergy, are exhibited exclusively in human beings, the few similar phenomena that have been noted in lower animals being of doubtful significance. For this reason the phenomena of allergy have been less susceptible to experimental analysis than are those of anaphylaxis, with the natural result that our ideas as to the nature of the former processes have, for the greater part, been reached through the medium of analogy. Repeated uncritical reference, in the literature, to the analogies, some of which, indeed, are most plausible, between the phenomena of allergy and those of anaphylaxis, have almost submerged the important restrictive criterion of the latter condition: namely, the demonstrated antibody-antigen nature of the reacting substances that are responsible for the symptoms of it, and those references have served only to cloud an otherwise clear and firmly grounded conception of anaphylaxis without, as yet, solving the question of the nature of allergy.

Allergic symptoms, like those of anaphylaxis—if the local reaction of Arthus can be considered as the result of an antigen-antibody reaction and, therefore, a true symptom of anaphylaxis—are general and local, the latter being more frequently observed and more widely studied than the former. The local † expression of allergy presents a variety of form comprising many of the clinical types of skin eruptions as well as subcutaneous edema and congestion of mucous membranes, together with the physiological consequences of such congestion, such as

* As has already been said, the term "allergy" was originally used by von Pirquet in a sense corresponding with the present one of anaphylaxis, and its application was afterward extended by Doerr to include all of the phenomena of altered reactivity whether to antigenic or to non-antigenic substances.

** The proposed use of this term is different from that which its originator had in mind, in that von Pirquet applied the word only to antigenic substances, whereas the present application of "allergen" must include, also, non-antigenic substances.

† It is convenient, as well as customary, to consider also the widespread skin eruptions that follow internal administration as a local phenomenon. This may be done on the apparently good ground that the effect corresponds with that which could be produced by the local application of the agent (in the case of the drug idiosyncrasies) to all of the affected areas.

hypersecretion and irritation of the nerve endings present in the area involved. The general symptoms include chill, fever, dyspnea, vomiting, fall of blood-pressure, loss of consciousness—a fatal issue sometimes resulting.

The allergens are of widely various nature, some possessing antigenic property, many lacking this property completely; some being directly poisonous when administered in sufficient amount, such as some of the drugs and chemical substances, others being entirely harmless to most individuals even when administered in large quantity, for example, the horse serum of diphtheria antitoxin, food substances or the various pollens.

It was natural, on the one hand, that the allergic phenomena induced by poisonous substances should be connected, in the minds of the investigators of those phenomena, with the directly poisonous properties of the exciting agents and, on the other hand, that the allergy induced by antigenic substances should be referred to the antigenic property of these substances. As a matter of fact, some investigators have believed that the drug idiosyncrasies represent only an exaggerated susceptibility to the usual physiological action of the respective agent, while the writers on serum allergy are unanimous in their acceptance of the explanation of that phenomenon that was offered by von Pirquet and Schick: namely, that the symptoms are caused by a reaction between the serum antigens and their specifically related antibodies. The former of these two ideas has been already abandoned; the latter, as will be presently shown, is not only not proved but, in view of a large body of evidence, may be considered questionable.

The consequence of this total difference in conception of the mechanism underlying the allergic phenomena of the drug idiosyncrasies and those of "serum disease" has been to divert attention from the remarkable parallelism between the clinical manifestations of these two groups of phenomena as well as the conditions operative in their causation, and, therefore, to discourage any suggestion of a possible identity of mechanism in both. While there is no direct experimental evidence of such identity, it would seem profitable, at least, to entertain the suggestion of an identity, based on the recognition of the numerous points of similarity between the two phenomena. Moreover, this conception is naturally to be extended to include consideration of the other groups of allergic phenomena, with the same purpose in view. In support of this suggestion it may be pointed out at once that no convincing evidence exists that the allergy to antigenic substances depends at all upon their antigenic property. The positive theory of von Pirquet and Schick in this respect is based on inference, not on an experimental demonstration.

The arbitrary nature of the classification of the allergic phenomena that is now employed is evident in the fact that the exciting agents have been grouped according to their relation to human use or to their biological origin. Thus, we have "drug idiosyncrasies," "hay fever," "food idiosyncrasies" (the latter two being grouped under the heading

of "human sensitizations"), "dermatitis venenata" and "serum disease."

Before the discussion of the similarity of these phenomena is undertaken it will be necessary to review the principal facts relating to them.

Drug Allergy (*Idiosyncrasy*).—A drug allergy is a condition of hypersensitiveness to a drug such that an effect of an unusual yet characteristic nature is produced by a quantity of the substance which, for most individuals, lacks appreciable toxic action.

A striking and noteworthy feature of the list of exciting agents considered under this category is its heterogeneity, the membership in this group being determined not by the criterion of chemical relationship but by the sole criterion of medicinal use. The list includes representatives of the metals (mercury, arsenic), the halogens (bromids and iodids), the alkaloids (quinin, morphin, strychnin, belladonna, hyoscyamus, stramonium), methane derivatives (iodoform), coal-tar products (antipyrin), benzol derivatives (salicylic acid, creosote, salol), also, resins, turpentine, sandalwood oil, cubebs, copaiba balsam and other drugs.

The separation of the drug allergies from those due to agents not used in medicine has, thus, no reason based on a special constitutive nature of the substances classed as drugs, and we shall see that there are no peculiarities in the clinical manifestations of the drug idiosyncrasies sufficient to stamp these as essentially different, in their underlying mechanism, from the idiosyncrasies to the non-medicinal substances—food or other. The separation is, in fact, upheld chiefly by custom and also by a certain convenience to the student of the general subject of idiosyncrasy.

The exciting agents responsible for the drug allergies possess, in common, a greater or less degree of toxicity, which is quantitatively and qualitatively constant for most persons, a certain small percentage of individuals, however, exhibiting a hitherto unexplained tolerance for ordinarily toxic doses of the drugs. While this ordinary toxic action is constant, in its physiological effect, and, therefore, in the resulting objective and subjective symptoms, for any one of the medicinal agents, it differs in the different drugs in a constant and characteristic way. The toxic action of mercury, for example, is characteristic and always distinguishable from that of morphin, strychnin or the bromids.

This "specificity" of the normal toxic action of the drugs is not apparent in the manifestations of their peculiar effects on hypersensitive individuals; witness, for example, the high fever produced in hypersensitive persons by the antipyretics. Indeed, the most striking and significant feature of the clinical manifestations of drug allergy lies in the fact that while they present a great variety of form, with minor exceptions,* none of those forms is characteristic of any drug nor class of drugs. On the one hand, a drug may cause, in different hypersen-

* These include the "fixed pigmented erythema" reported, hitherto, only in the allergy to antipyrin, phenacetin and salipyrin and the herpetic eruption of arsenic and antipyrin.

sitive individuals, different clinical manifestations, while, on the other hand, any one of these different manifestations may be produced by a number of different drugs. A corollary of this important peculiarity of the symptoms of drug idiosyncrasy is the fact that, with the possible exception of the acne of bromids and iodids, the ordinary toxic effects of the drugs are entirely different from the effects of ordinarily non-toxic quantities of the same drugs on the hypersensitive individual.

The only conclusion that can be drawn from these facts is that a drug does not produce its peculiar effect upon the hypersensitive person through the usual medium of its toxic action, but through a different mechanism, which is the same in all of the drug allergies.

SPECIFICITY.—Drug allergy is, to a certain degree, specific; that is, it is exhibited, in most hypersensitive individuals, to only one substance or chemical group. This principle need not be altered because of the fact that exceptionally an individual is found to be hypersensitive to more than one drug,^(a) such a case being, no doubt, an instance of specific hypersensitiveness to each of the different drugs.

The investigation of the specificity seen in drug allergy, unlike that of antigenic specificity, has led to the well-founded conclusion that the former is often referable, not to the entire molecule of the substance, but to a certain element or chemical group contained in it. Thus, the idiosyncrasy to the mercurial compounds does not depend on the halogen entering into them but to the element mercury; the allergy to iodoform does not extend to the iodids nor to iodine but depends on the methyl group, since it is exhibited, also, to some of the chlorine and bromine derivatives of methane as well as to di-methyl sulphate and the methyl ester of toluene sulphonic acid, whereas the iodine substitution products of compounds containing three or more carbon atoms are inactive. An iodine hypersensitiveness does, however, exist, it being exhibited to iodids, not to the chlorides of the same metals. No hypersensitiveness to potassium chloride has been recorded, though chlorate allergy exists. Wechselmann^(b) reports a case of allergy to salvarsan in which neosalvarsan caused no symptoms and this author states that similar instances were encountered by Gennerich.

INCUBATION PERIOD.—In most cases the symptoms of drug allergy appear within a few hours after the administration of the drug. There are, however, a number of instances of relatively recent record in which the symptoms of drug allergy appeared after intervals of from 5 to 20 days following a primary injection.^(c) In such cases a subsequent injection was usually, though not always,^(d) followed by a recurrence of the symptoms. In one case^(e) the incubation period was missing at the reinjection, an "immediate reaction" occurring.

In many individuals, after several or even a large number of administrations, none of which have been followed by symptoms of allergy, a further administration causes an immediate "attack," the hypersensitiveness thereafter persisting or disappearing completely. Under

References: (a) 160. (b) 244. (c) 245, 207, 212, 63, 166, 163, 143, p. 521. (d) 212. (e) 207.

such circumstances it is difficult or impossible to determine the true incubation period of a drug idiosyncrasy, because of the possibility that the last dose given before the onset of symptoms was not the one that initiated the incubation period. Thus, in Wechsellmann's case^(a) of hypersensitiveness to *Fagara flava*, which may be included with the drug allergies, the cabinet maker was attacked with a dermatitis of the forearm, face and neck eight days after he had begun to work with that wood. During the days of this period the patient had been constantly exposed to the influence of the exciting agent in the wood; however, this circumstance does not exclude the possibility that the outbreak of the dermatitis was determined, in point of time, by the interval succeeding the first exposure and, furthermore, that this interval was not affected by the subsequent exposures.

FEVER.—Fever, sometimes preceded by a chill, is one of the most frequent symptoms of drug allergy, being also paradoxically present, in marked degree, in hypersensitiveness to the antipyretics, such as quinin and antipyrin. The course of the fever has not been given particular study. Temperatures as high as 104°-106° F. have been recorded in hypersensitiveness to iodids, mercury, salicylic acid and antipyrin, and in one instance of quinin allergy the temperature reached 108° F.

Fever is often present without eruption in quinin allergy and sometimes, also, in the allergy to other drugs such as the iodids and mercury. On the other hand, the symptom of fever may be absent in the presence of a drug eruption. There is, thus, no causal relationship between the eruption and the fever in drug allergy, these two symptoms being due to a cause that underlies both of them.

ERUPTION.—The different forms of the eruption of drug allergy are too numerous to receive individual consideration here. The most common of these are the erythematous, the urticarial, the vesicular, the maculopapular or papular and the hemorrhagic. While all of these forms have been encountered, in one case or another, in the idiosyncrasy to each of a number of drugs (for example, chloral, iodids, arsenic, quinin, salicylic acid, antipyrin, iodoform and copaiba balsam), one or another form is missing in the records of idiosyncrasy to some other drugs—such as the bromids, belladonna and corrosive sublimate, which apparently have not produced a hemorrhagic eruption, or digitalis and potassium chlorate, to which, thus far, no vesicular eruption has been credited. However, the conclusion is by no means warranted that the missing forms cannot be produced by the respective drugs. It may be, indeed, that those drugs have already produced the missing forms of eruption in cases which, for one reason or another, have not been placed on record.

Although it is true that all of the agents of drug allergy are capable of producing most of the different forms of the eruption, a certain tendency is, nevertheless, apparent, on the part of some drugs, to cause a particular form of eruption, though not at all to the exclusion of the other forms. Thus, arsenic is especially prone to cause a herpetic eruption, this form being occasionally produced, also, by antipyrin.

While it was early observed that different individuals react differently to the same drug, it was, for a time, believed that the same individual always reacts in the same way to the same drug.^(a) This belief is no longer held.^(b) The form of the eruption does not remain constant on repeated administration, nor does the intensity of this symptom always remain the same; it may increase, or diminish even to the vanishing point.

The drug eruptions are generally accompanied by itching. Pruritus may exist without eruption.

A peculiar form of eruption, noted, heretofore, only in the allergy to antipyrin, phenacetin and salipyrin, is the "fixed pigmented erythema,"^(c) which in successive allergic attacks recurs always in the same place. This phenomenon was explained in an experimental study by Apolant,^(d) who showed, by the local application of the respective drug, that the skin at the site of the fixed eruption was hypersensitive, whereas the remaining skin surface was insensitive to the direct action of the drug.

The mucous membranes are rarely, if ever, involved by the eruptions of drug allergy, the ulceration of these surfaces reported in opium idiosyncrasy being, perhaps, an instance of such involvement. Indeed, the mucous membranes have been proven to be entirely insensitive to the local application of iodoform in a case of extreme hypersensitiveness of the skin to that drug.^(e)

OTHER SYMPTOMS.—Beside the chief symptoms of eruption and fever there are other less frequent or, at any rate, less frequently noticed symptoms in drug allergy, of which may be mentioned edema, especially of the face (seen in the allergy to digitalis, opium, chloral, antipyrin, salvarsan); a local edema or sterile abscess or gangrene occurring at the site of injection; joint swelling^(f) and swelling of the lymph-nodes.^(g)

Changes in the blood-pressure and in the number of the leukocytes in the peripheral blood during the "attack" of drug hypersensitiveness have received almost no study. Heran and Saint Girons^(h) report a distinct lowering of the blood-pressure and a leukopenia after the administration of quinin in a case of allergy to this drug.

The disappearance of a once established drug idiosyncrasy is a rare occurrence and it has almost always happened under circumstances that were not in the control of the observer. Lewin, however, states that the tolerance which sometimes intervenes in the allergy to the iodids is chiefly the result of a "change of dosage." The condition of tolerance induced by Jadassohn⁽ⁱ⁾ in a case of allergy to mercury bears a remarkable resemblance to desensitization in anaphylaxis. The external application of calomel to the skin caused in the patient a local eruption. A subsequent internal administration of a different mercurial preparation produced a general eruption, which, however, did not affect the areas previously treated with the calomel. By the ad-

References: (a) 32. (b) 143, p. 29. (c) 90, p. 656. (d) Cited by Doerr, 76. (e) 123, 168, 42. (f) 163 (g) 119. (h) 123.

ministration of gradually increasing amounts of mercury the patient was brought, at last, to a state of insensitiveness to mercury however it was applied.

In the recently reported case of Heran and Saint Girons ^(a) insensitiveness seems to have been produced, in a case of quinin allergy, likewise at will and with a procedure closely simulating that of desensitization in anaphylaxis. In fact, the authors wish to identify the resulting state of tolerance as one of "antianaphylaxis." The patient had contracted malaria and the administration of quinin was, therefore, indicated. In this respect, however, a difficulty existed on account of an idiosyncrasy to quinin, which had been first noted four years previously and again, two years later, when the patient had been given that drug. The authors first verified the existence of the allergy by administering 0.25 gram of quinin sulphate, this quantity of the drug causing a repetition of the violent symptoms (dyspnea, general urticaria) that had followed the earlier administrations. The drug was then given according to the following plan:

First day (i.e., the day after the test dose had been given)	9.45 A. M.	0.005 gram
	11.15 A. M.	0.1 "
Second day	at first	0.005 "
	later	0.2 "
Third day		0.4 "
Fifth day		0.8 "
Sixth day		0.8 "
Seventh day		1.0 "

No symptoms followed any of these administrations of the drug and the patient was cured of his malaria.

Heran and Saint Girons conclude that quinin hypersensitiveness is actually a condition of anaphylaxis; first, on account of the resemblance of the symptoms to those of anaphylaxis, among which they mention a fall of blood-pressure and a leukopenia; secondly, on account of the analogy between the process of desensitization by the administration of sublethal doses of antigen and their procedure in inducing the tolerance to quinin. The authors admit that their attempts passively to transfer the quinin hypersensitiveness to lower animals failed. However, they look upon this failure as corresponding with the occasional failures of passive transfer in anaphylaxis.

The importance of the evidence obtainable with the technic of passive transfer had already been recognized and a number of experimenters had applied this technic in the study of the etiology of drug allergy. The first experiments ^(b) were apparently successful inasmuch as immediate symptoms were produced by the intravenous injection of the respective drugs into the animals which had received injections of the hypersensitive individuals' serum. However, more critical analysis of the experiments showed the results to be wholly unconvincing, chiefly

because of the fact that none of the animals died of the immediate effects of the injection, whereas all of them, as well as all of the control animals, died from the ordinary toxic effect of the drug, no difference, in this respect, being exhibited in any of the animals. Moreover, the "immediate" symptoms noted in these experiments were in no case shown to depend upon the anatomical changes that are regularly found in anaphylactic shock.

Finally, passive transfer of drug hypersensitiveness to animals has failed in many hands ^(a) and even with those who, at first, reported successful experiments. ^(b)

In view of the obvious and possibly exclusive importance of individual "predisposition" in the etiology of drug idiosyncrasy it would seem, *a priori*, unlikely that drug hypersensitiveness could be experimentally induced in lower animals, and the numerous negative experiments of Auer ^(c) and of Lesne-Dreyfus in the attempted active sensitization of guinea pigs and rabbits with salvarsan are in harmony with this presumption.

Undeterred either by the theoretical consideration referred to or by the published, negative experiments, Swift ^(d) undertook the active sensitization of guinea pigs with salvarsan. In his experiments Swift introduced a slight technical modification, inasmuch as he first mixed the drug with normal guinea pig's serum before injecting it, this mixture being used both for the sensitization and for the test injection. The use of the mixture was based on an assumption that the serum was altered by the salvarsan in some unexplained way so that it became endowed with the antigenic property of a "foreign" protein. Swift thus adopted the theory of Wolff-Eisner as to the nature of drug allergy, namely, that the hypersensitiveness is not directed against the drug itself but against a modified form of the individual's own proteins. Without attempting to explain the small proportion of positive results obtained by Swift, we would point out that in order to elicit the symptoms of drug allergy it is never necessary to mix the drug with the individual's serum before administering it.

Wolff-Eisner's theory of the nature of drug allergy is opposed first, by the fact, pointed out by Doerr, ^(e) that its application must be restricted to the few elements with which a chemical combination of proteins is known to be possible and secondly, by the failure, hitherto, to demonstrate, with the anaphylaxis reaction, a constitutive specificity in such combinations different from that of the original protein. Furthermore, the theory takes no account of the factor of predisposition, which is so evident in the cases in which the allergy is exhibited at the first exposure to the drug.

The localization of the eruption in the cases of "fixed pigmented erythema" and particularly the demonstrated insensitiveness of the mucous membranes in iodoform allergy has naturally suggested a cellular nature of drug hypersensitiveness. Bloch ^(f) has experimentally investigated this question by carrying out two Thiersch skin-grafts upon a

References: (a) 233, 282, 195. (b) 48, 131. (c) 16. (d) 224. (e) 76. (f) 42.
VOL. I.—11.

surface denuded by a burn, one graft being taken from an individual that was hypersensitive to iodoform, the other being derived from a normal person. After the grafts were well established on the foreign soil iodoform was sprinkled on both of them and kept in contact with them by means of a bandage. During the first four days of this continuous contact no difference was noted in the appearance of the two grafts. On the fifth day the graft from the hypersensitive individual presented a vesicle formation and in four or five days it became necrotic and was discharged. The normal graft maintained a healthy appearance until five days after the first changes appeared in the other one, but then it, also, began to degenerate and was soon discharged.

Doerr accepts this experiment as indicating the cellular nature of the drug hypersensitiveness, without, however, noting the fact that whereas the symptoms of idiosyncrasy to iodoform appear within a few hours after its application to the skin, the transplanted graft taken from the hypersensitive individual in Bloch's experiment remained unaffected until the fifth day. It seems, indeed, more probable that the changes in this graft were not caused by the action of the iodoform but represented the usual course of such grafts, which, as Bloch himself remarks, are, as a rule, discharged within two to four weeks after the transplant has been made. In this instance the graft from the hypersensitive person was not discharged until 16 or 17 days after it had been transplanted. This experiment has not been repeated, and the underlying idea of a cellular nature of drug idiosyncrasy has not been considered in the subsequent literature.

The influence of inheritance in drug allergy has not been investigated. There are a few recorded instances of allergy to the same drug in parent and child as well as in sisters.^(a) Our further knowledge as to this factor consists merely in the observation that in some individuals the allergy is present at birth, while in others it develops after varying periods of intermittent exposure to the influence of the drug. These latter instances are generally referred to as those of "acquired" hypersensitiveness, which implies that the development of the allergy is, in some way, determined by the previous exposure to the drug. However, in the light of the recent extensive research of Cooke and Vander Veer^(b) upon the operation of the factor of heredity in the etiology of the "human sensitizations" it does not appear necessary to assume that the previous exposures contributed to the establishment of the state of hypersensitiveness.* The time of onset of the condition may, here also, be determined entirely by hereditary influence.

Serum Allergy (*Serum Disease*).—The earliest observations on the unpleasant effects that follow the injection of foreign serum and which are now generally referred to as serum disease, were made late in the period, beginning with the first operation of Denis in 1667, in which the transfusion of the blood of lower animals (lamb's blood)

* By this is meant the state in which, with or without a period of incubation, the administration of a drug is followed by the characteristic symptoms of allergy.

References: (a) 143, pp. 402 and 463. (b) 62.

was practiced as a therapeutic measure. The first of these observations was that of Dallera, who, in 1874, described a general urticarial eruption occurring 10 days after the transfusion. As the operation of lamb's blood transfusion was only infrequently resorted to, the number of the reported instances of such effects was correspondingly small. With the advent of antitoxin therapy in 1894 the injection of foreign serum became a common practice and immediately the number of the observed and reported cases of "serum disease" was greatly increased. However, the authors at the beginning of this period, disregarding or perhaps unaware of the earlier observations, believed that the symptoms were caused by the antitoxin contained in the serum. This error was quickly corrected by Johannessen,^(a) who produced the same effects by injecting normal horse serum. Whether the symptoms that occur after the injection of antitoxic sera are ever due to the contained antiseptic has not been experimentally investigated. That the preservative is not always responsible for the symptoms seems to be proven by the instances observed in the earlier transfusion period.

After a large number of cases had been recorded the symptomatology was summarized and the question of the frequency of the condition was treated in two extensive researches by Hartung^(b) and by Daut,^(c) both of whom, also, investigated the important question of the incubation period in a considerable series of cases. It is convenient, first, to review the facts relating to serum allergy from the point of view of their presentation in these publications.

FREQUENCY.—The estimation of the relative frequency of serum disease varies greatly in the different recorded series of cases; in the three series of 61, 35 and 26 cases injected by Hager, Bachmann and Rumpf, no instances of serum allergy occurred, and in Unruh's series of 180 cases, the incidence of symptoms was only 2.22 per cent.; whereas, on the other hand, Heubner, Timmer and Park and Throne observed 28 per cent., 20 per cent. and 59 per cent. in series of 77, 147 and 100 injections respectively. Even the estimations drawn from large series are far from concordant. In Hartung's series of 2661 cases collected from the literature, the incidence was 11.4 per cent. Daut noted symptoms in about 10 per cent. (39 times) of his series of 400 injections. The German imperial department of health, on the other hand, reported only 8.1 per cent. of reactions in a series of 4358 cases, while Goodall,^(d) in a series of 10,000 injections, records as many as 35 per cent. of eruptions, and Axenow,^(e) in a series of 1032 injections, observed 66 per cent. of eruptions.

INCUBATION PERIOD.—The earlier records of the antitoxin period are particularly useful with respect to the question of the incubation period, because there could be no reasonable uncertainty as to whether the patients had had previous injections of horse serum.

The incubation period of serum disease following a first injection of serum varies from three hours (in one case of Daut's) to 24 days (one case of Hartung's). In Hartung's series a notable proportion

(32.8 per cent.) of the eruptions appeared between the 10th and 12th days and since a similar proportion of the cases of Heubner and Bokai (together 13 out of 42) began to show symptoms on the 11th or 12th day, Hartung referred to these as "critical" days, in which the first symptoms are especially prone to occur. However, it should not be overlooked here that, in as many as 23.4 per cent. of Hartung's cases of serum disease, the symptoms appeared within the first three days.

The question of the incubation period in serum allergy will be reverted to in the discussion of the theory of von Pirquet and Schick regarding this condition.

FEVER.—Elevated temperature, though a frequent accompaniment of the eruption of serum disease, is not constantly associated with that symptom. In Hartung's series it was absent in 24 per cent. of the cases that presented an eruption. The degree of the fever is often considerable, reaching, in two of Hartung's cases, as high as 106°–106.5° F. The duration of the fever corresponds, in the main, with that of the eruption with, however, numerous exceptions. The highest point of the fever may be reached as early as two days before the appearance of the eruption, or as late as the eighth day of the rash. However, this climax is most common on the day of the appearance of the rash or on the day previous to its appearance. In some instances the fever is present only on the day preceding the appearance of the eruption, after which the temperature remains normal. The course of the fever is usually of remittent type, though sometimes it is intermittent.

ERUPTION.—The eruption of serum allergy is highly polymorphous, different forms often occurring at one time in the same individual. The different anatomical forms encountered are the erythematous, the intensely itching urticarial, the papular or maculopapular, the vesicular and the hemorrhagic. The chief clinical types are the scarlatiniform, the morbilliform and the so-called erythema exudativum multiforme. The serum eruption is local; that is, occurring about the site of injection, or general, involving, symmetrically, all parts of the skin surface.

Local Eruption.—Generally speaking, the local eruption seems to appear earlier than the general eruption. In no instance observed by Hartung did a local eruption appear later than the 6th day after the injection, and 71.4 per cent. of such eruptions were present by the 2nd day. Baginsky, however, saw a local eruption appear as late as the 10th or 12th day and in Unruh's series most of such eruptions occurred between the 7th and the 22nd day. According to Hartung, the local eruption is generally unaccompanied either with fever or with subjective symptoms. The local eruption is usually followed by a general eruption. However, according to von Pirquet and Schick, the general rash may be missing. A considerable interval of time may separate the appearance of the local eruption and that of the general eruption—as much as 13 to 20 days in some cases.

General Eruption.—This often appears in "crops" over several days. There is, also, a distinctly recurrent form of the general eruption, which may be separated from the first general eruption by a con-

siderable interval of time that shows, however, no constancy (5-21 days), although in Hartung's collected series a large proportion of the recurrences took place after an interval of about two weeks.

MUCOUS MEMBRANES.—Very exceptionally the mucous membranes appear to be involved in serum allergy. The angina-like changes in the throat described by Hartung were not seen in any case by von Pirquet and Schick, and the conjunctivitis and rhinitis of Hartung could not be referred, by von Pirquet and Schick, to the serum injections. The latter authors, however, are inclined to believe that the bloody diarrhea noted in two of their cases, like the diarrhea noted in three cases by Hartung, were due, in some way, to the injection of the serum; they noted, also, elevated, reddened spots on the conjunctiva during the serum eruption in two cases.

JOINTS.—Pain and tenderness in the joints occur in serum allergy, being found in from 1 to 1.9 per cent. of all injected individuals. The metacarpophalangeal joints appear to be more frequently affected^(a) than other joints. Hartung reports some cases in which swelling of the joints was a prominent accompaniment of the pain. Von Pirquet and Schick, on the other hand, state that it is just the absence of objective joint symptoms that characterizes the painful condition of the joints in serum disease. They observed no instance of swollen joints in their series. Besides the joint pains there are sometimes observed rheumatoid pains in the muscles.

EDEMA.—This symptom of serum allergy, though previously observed, was given particular study by von Pirquet and Schick, its extent being determined with the method of von Pirquet, which consists in estimating the amount of edema from the increase in body weight. These authors found that the edema is sometimes associated with albuminuria and they pointed out the fact, which distinguishes the edema of serum disease from that of nephritis, that in the former condition the edema appears before the albuminuria, whereas in nephritis this order of appearance is reversed. The edema of serum allergy is, thus, not of renal origin. The edema of serum disease, like that of nephritis, affects most commonly the face, especially the eyelids and also the dependent parts of the body. It disappears with the other symptoms of the condition.

The albuminuria of serum disease is always slight, according to von Pirquet and Schick not over 1/40 per cent.

LYMPH NODES.—Enlargement of the lymph nodes was noted in serum disease by the earlier authors, but von Pirquet and Schick ascribed to it a special importance as one of the most constant of the symptoms and, furthermore, as useful in prognosis inasmuch as it makes its appearance before any of the other symptoms and it is the first symptom to subside. The enlargement, which is accompanied by pain and tenderness, affects chiefly, and sometimes only, the regional nodes, a general adenitis, however, occasionally occurring.

LEUKOPENIA.—The changes in the leukocyte content of the blood in

serum disease were first studied by von Pirquet and Schick, who observed that when any noteworthy alteration did take place in this respect it was always a diminution in the total number of the leukocytes at the expense of the polynuclear cells.

HEREDITY.—Whether heredity is a factor in the etiology of serum allergy has not been investigated. Von Pirquet and Schick mention an instance of sisters being subjects of serum allergy and they assume, in this case, a family disposition.

THEORY OF THE MECHANISM OF SERUM ALLERGY.—Previous to the appearance of the well-known publication of von Pirquet and Schick ^(a) there had been no generally accepted explanation of the phenomena of serum disease. The idea that the effects observed were due to antitoxin ^(b) had been dispelled by the experiments of Johannessen, ^(c) which have already been referred to. Other suggestions had been: (1) that the eruption is due to a mechanical blocking of the capillaries, either with the particles that are sometimes present in antitoxic sera (portions of blood corpuscles, fibrin shreds) or with clots formed in the patient's blood under the influence of the injected serum; ^(d) (2) that the eruption is due to local changes in the tonus of the vessels, and thus represents a form of angioneurosis. ^(e)

Hamburger and Moro, ^(f) having demonstrated precipitin formation in human beings that have received injections of horse serum, conceived the idea that the symptoms of serum allergy are due to the mechanical interference with the circulation by a specific precipitate formed, *in vivo*, by a union of the injected horse serum and the precipitin present in the patient's blood. This theory was abandoned after Rostoksi ^(g) and Michaelis and Oppenheimer ^(h) had apparently shown that specific precipitates do not form *in vivo*.

The study of von Pirquet and Schick was devoted to the establishment, by means of clinical and experimental evidence, of their theory that the symptoms of serum allergy or "serum disease," as they called it, are produced by a toxic substance that results from the interaction of newly formed antibody with persisting traces of circulating antigen, that is, horse serum.

The clinical evidence presented by these authors consists: first, in the common observation that the symptoms of serum allergy generally appear after an incubation period, which, in a considerable proportion of the cases, ends between the 8th and the 12th days; secondly, in the observation, reported by these authors, that after a second injection of serum the incubation period was found, in some instances, to be shortened or even lacking, the symptoms appearing immediately after the injection; thirdly, in the further observation by von Pirquet and Schick that a local edema sometimes occurs at the site of a reinjection of serum, this phenomenon being considered by the authors to be due to a local antibody-antigen reaction.

References: (a) 241. (b) 120, 143. (c) 126. (d) 117. (e) 165. (f) 205. (g) 161.

It will be instructive to subject the foregoing three points of evidence to critical examination.

Incubation Period after a First Injection.—In pointing out that, in a considerable proportion of cases, the incubation period following a first injection of serum lasts from 8 to 12 days, von Pirquet and Schick press two arguments in support of their theory. The first of these is the inference that there is a significant regularity in the length of the incubation period of serum allergy and the second is that the length of this incubation period is approximately the same as that which precedes the appearance of specific antibodies after the injection of a foreign serum. If these two arguments could be upheld they would offer, indeed, considerable support for the theory of von Pirquet and Schick, inasmuch as an antibody-antigen reaction would remain a plausible possibility as the cause of serum allergy.

As a matter of fact, however, both arguments appear to be all too weakly founded.

As to the inference of regularity in the duration of the incubation period, it is obvious that such a claim could be made only by altogether ignoring a large proportion of the reported cases, since in 24 to 48 per cent. of all cases of serum disease the incubation period is of less than 8 days' duration, while in about 14 per cent. the incubation period is longer than 12 days.

In an apparent effort to identify the particular incubation period of 8 to 12 days, which they had selected, with that of antibody production, von Pirquet and Schick published the curve of precipitin production as observed by them in a rabbit that had received an injection of horse serum. In this instance, the first appearance of precipitin in the animal's blood was noted on the 9th day, the height of the curve being reached on the 12th day. Similar results, in this respect, had been obtained by Hamburger and Moro,^(a) who noted the first appearance of antihorse precipitin in two rabbits on the 8th or 9th day, the antigen disappearing from the circulation at about the same time.

If it could be shown that in a large proportion of cases the duration of the incubation period of serum disease coincides with that of precipitin production in human beings, this observation would be wholly unavailable for the explanation of the fact that in some instances of allergy occurring after a first injection of serum there is an entire absence of incubation period. Such instances offer, at once, an unsurmountable obstacle to the acceptance of the theory of von Pirquet and Schick.

With a demonstrated coincidence of the incubation period of precipitin production in human beings and that of the usual phenomenon of serum allergy, the theory of von Pirquet and Schick could be brought into agreement with the instances of recurrent eruption after a first injection by assuming that the first eruption marked the appearance of the partial antibodies, say, to serum globulin, while the second eruption could be ascribed to the later appearance of other partial an-

tibodies (to serum albumin or other antigenic constituent of horse serum). As a matter of fact precipitin to egg globulin is produced by rabbits earlier than that to crystalline egg albumen.*

Furthermore, it seems to be actually true that the "recurrent" symptoms occur only when more than one of the serum components are injected. The writer, in a study of 1519 injections** of the isolated pseudoglobulin of horse serum (the purified antitoxin of Atkinson-Gibson as prepared by the Board of Health of New York City), encountered 8.5 per cent. of eruptions, but among these cases of serum allergy—129 in all—there was not a single instance of recurrent symptoms.

However, the theory is embarrassed by the fact that no constant relation could be established between the onset of the symptoms of serum allergy and the process of precipitin production in human beings, because:

(1) The symptoms generally preceded the appearance of precipitin, often by a considerable period,^(a) and they sometimes disappeared while precipitin and horse serum were still present together in the patient's blood.^(b)

(2) The symptoms sometimes continued after precipitin was no longer demonstrable and they occurred in individuals in whom no precipitin production could, at any time, be demonstrated.^(c)

We are indebted to C. W. Wells^(d) for an extended study of the curve of precipitin production in human individuals. This investigator found no constant relation between the amount of serum injected and the incubation period of precipitin production, nor the duration of the period of precipitin production, nor the amount of precipitin formation (highest concentration attained by the blood). He also showed that the incubation period, which, in his cases as in those previously reported, varied greatly, is sometimes as short as four days.

However, Wells, in agreement with von Pirquet and Schick, was unable to show a constant coincidence of the onset of the symptoms of serum allergy with either the appearance of the precipitin in the blood, or the attainment of a high concentration of this body in the circulating fluid, or its disappearance herefrom.

Such inconsistencies were met by von Pirquet and Schick with the assumption that the antibodies concerned in the causation of serum allergy are different from precipitin. Such an assumption, however, is still lacking in experimental support. Indeed, the antibody responsible for the only other known "vital" antibody-antigen reaction (the reaction of anaphylaxis, with which, by the way, serum allergy is held, by practically all investigators of the subject, to be related) has been shown^(e) to be indistinguishable from precipitin.

In explanation of the cases of serum allergy without precipitin

* Unpublished experiments of the writer.

** Acknowledgment is due Dr. William H. Park and Dr. R. J. Wilson for permission to use these data, which were obtained from the records of the Willard Parker Hospital, New York City.

References: (a) 116: 16 days in one case of Hamburger and Moro. (b) 241, pp. 109, 116, 141. (c) 94, 269. (d) 268. (e) 78, 138, 256, 76, p. 1021.

production the authors remark that the "vital" reaction of serum disease is a much more delicate criterion of the processes of immunity in the body than is the test-tube experiment. However, a serious difficulty is offered to such an explanation by the numerous cases in which precipitin production *without allergy* follows the serum injection.^(a)

It is true that a plausible explanation of the instances of precipitin production without allergy may be based on the possibility, discussed in the section on anaphylaxis,* that the antibodies responsible for the condition of anaphylaxis are not of one quality. It could be assumed, on this basis, that the precipitins supposed to be concerned in the causation of serum disease are of a peculiar quality that is possessed in less degree by other precipitins, and that it is these latter less active precipitins only which are found in the cases just referred to.

However, this explanation stretches the analogy of the conditions in anaphylaxis too far beyond the facts of these conditions. Actually, the content in sensitizing antibodies of immune sera that have been produced with relatively few injections has been found to be *constantly parallel with their precipitin content*, the latter being determined with a method identical with that used in the examination of human sera—a method which does not distinguish precipitins of different qualities. No instance is known of a distinctly precipitating serum that, when obtained under the usual circumstances and used in a fresh condition, lacks corresponding sensitizing power; in other words, the precipitin of the lesser sensitizing power never appears unaccompanied by the precipitin of the greater sensitizing power.

In their recent publication upon the relation of circulating antibodies to serum disease, Longcope and Rackeman^(b) conclude that no precipitin nor "anaphylactin" is formed in human individuals that are not subject to serum disease. This conclusion, however, is drawn from the negative results of the examination of only three such individuals with each of the two methods. These few negative findings can carry no weight against the positive results obtained by Francioni^(c) in four of his injected cases that did not develop serum disease, and especially against the 18 similar cases reported in the painstaking study of C. W. Wells.^(d)

Longcope and Rackeman found that, in some of their cases, recovery from the symptoms of the serum allergy was preceded by the appearance of antibodies in the blood and, on the basis of this observation, they concluded that the disease is terminated by the neutralization of the *circulating* antigen (horse serum) by the antibodies. Here, also, the authors' conclusion appears to rest on insufficient evidence, since von Pirquet and Schick,^(e) Francioni, Lemaire^(f) and also C. W. Wells^(g) report a number of instances of serum disease in which the possibility of such a mechanism must be excluded, the antibodies either disappearing before the cessation of the symptoms, or appearing

* This volume, page 140.

References: (a) 94, 268. (b) 152. (c) 94. (d) 268. (e) 241. (f) 141. (g) 268.

only after a considerable interval following the subsidence of the symptoms, or being at no time present, as in two of the cases reported by Longcope and Rackman themselves.

The difficulties involved in the theory of von Pirquet and Schick would not be entirely removed even if a constant relation could be demonstrated between the symptoms of serum allergy and the presence of antibodies in the blood, because the sudden onset of the symptoms of serum disease is in disagreement with the gradual rise of the curve of antibody production, in human beings, from an initial low concentration, as seen in the cited study of C. W. Wells.

Incubation Period after a Reinjection.—Von Pirquet and Schick formulated the general principle that, owing to the altered reactivity of the individual's tissues, which had been brought about by the primary serum injection, the second injection is followed, more quickly, by the specific response, on the part of the tissues, that is responsible, as they believe, for the development of the symptoms of allergy. As the authors pointed out, this principle derived an important significance from the analogous observation of von Dungern^(a) that the incubation period of precipitin formation is regularly shorter after a second injection of the antigen than it is after a first injection. The allergy developing with a shortened incubation period following a reinjection of serum was designated by von Pirquet and Schick as an "*accelerated reaction*."

These authors formulated, also, the further general principle that if a second injection of serum is given during the period following the first injection, in which antibodies are still present in the individual, the symptoms of allergy develop immediately, that is, without incubation period. This effect they designated the "*immediate reaction*."

The period in which an "*accelerated reaction*" was caused by a reinjection of serum, in the experience of von Pirquet and Schick, began 3 weeks after the primary injection and such reaction was once observed to follow a reinjection undertaken as long as 7½ years after the first injection. The authors observed the "*immediate reaction*" after reinjections given in the interval between the 12th day and the 5th month following the primary injection. Thus the period of the "*immediate reaction*" overlaps somewhat that of the "*accelerated reaction*," which begins at the end of the third week, and it could be expected that individuals reinjected between 3 weeks and 5 months after the first injection might present both an "*immediate reaction*" and an "*accelerated reaction*." Actually, von Pirquet and Schick report five such cases of "*double reaction*."

A review of the authors' cases with reference to the phenomena just described reveals the fact that when any reaction occurred after a reinjection, it did so almost always before the 8th day, that is, before the "*critical days*" in the incubation after a first injection. In the authors' series of cases, therefore, the incubation period of the serum allergy was generally shortened after the reinjection. In this connection it is to be noted that in Daut's series of six reinjections the sym-

appeared in only one instance previous to the eighth day, while in one of these cases the period of incubation was as long as 16 days. In the series of reinjections reported by Goodall^(a) there are, also, several instances (cases 43, 56 and 81) of serum rash following a primary injection in which the reaction that resulted from the reinjection could not be considered as an "accelerated" reaction, since the incubation period in the three cases following the reinjection was respectively 6, 8 and 7 days.

However, the other observations of Goodall, taken together with those of Currie,^(b) confirm the rule laid down by von Pirquet and Schick insofar as they demonstrate in general a shortening of the incubation period at the reinjection. This is indicated by the following facts: Currie, in a considerable series of cases, showed that a reinjection undertaken within 10 days of the first injection exerts no influence upon either the normal incubation period, or the rash frequency, or the duration of the rash. In Goodall's series of 90 cases, 41 developed a rash following the first injection of serum and of these only three presented an incubation period of less than 5 days. On the other hand, a reinjection of the entire series was followed, in 30 cases, by a rash that appeared between the 2nd and 4th days after the administration of the serum.

Thus, it seems beyond doubt that in a large proportion of reinjections the incubation period is shorter than that following a primary injection. However, this effect is not always observed and, furthermore (it is important to bear in mind), *the effect is by no means shown to be dependent on any immunological process*. Caution against such an interpretation is urged by the fact that a similar phenomenon has been observed in the allergy produced by non-antigenic drugs.

The interpretation placed by von Pirquet and Schick upon the "immediate" reaction following a reinjection, as due to the presence of the antibodies that were induced by the first injection has not been supported by experimental study, and it would seem to be placed in question by the observation of Goodall that not any of the 22 individuals who were reinjected previous to the 35th day following the primary injection responded with an "immediate" reaction, although such reaction occurred in 16 individuals that were reinjected between the 35th and the 79th days after the primary administration of serum. It seems very unlikely that antibodies persisted in these 16 individuals, although in all of the 22 individuals the antibodies must be assumed, according to von Pirquet and Schick, to have disappeared at an earlier period.

It is clear from the protocols of von Pirquet and Schick as well as from those of other observers that an "immediate reaction" sometimes results from a first injection of serum and that it cannot, therefore, be always due to the presence of specifically induced antibodies. Such cases are analogous to those of drug allergy in which the symptoms occur immediately, or within a few hours after a first administration.

It is also demonstrated in Case 2 of their "experimental" Series I, page 80, that the reinjection of an individual, who has already responded with allergic symptoms to an injection given 20 days previously, need not result in either an "immediate reaction" or an "accelerated reaction." Actually, the reinjection caused no symptoms at any time. For this interesting case the authors have, they state, no explanation, and the embarrassment presented to their theory by the case is, naturally, not relieved by the subsequent observation of eight such cases by Goodall.^(a) Such cases have, indeed, no explanation within the limits of the theory of von Pirquet and Schick, but they have a perfect analogy in the experience of others with the allergy to the non-antigenic drugs.*

The interpretation placed by the Vienna investigators upon the "immediate reaction" following a reinjection of serum is, thus, an altogether unsupported inference that can hardly be brought into agreement with certain reported observations.

The "double reactions" of von Pirquet and Schick, consisting of both the "immediate" and the "accelerated" reaction, must be looked upon as identical with the "recurrent" reactions, which had already been described by several observers.^(b) Certainly, there is no criterion of separation of such cases other than the arbitrary one contained first, in the accidental occurrence of such recurrences, in von Pirquet and Schick's experience, after a second injection, and secondly, in the fact that the time interval between the appearance of the primary and the recurrent symptoms in the previously reported cases was often longer than that noted in any of the cases of von Pirquet and Schick.

The double or recurrent eruptions of the previous authors were observed to follow first injections of serum and the time interval between the two eruptions varied from 3 or 4 days, as in Daut's two cases, to as much as 19 or 21 days, as in two instances reported by Hartung. The primary eruption sometimes appeared within 24 hours after the injection, as in the instances reported by von Pirquet and Schick.

More recently Goodall ^(a) has reported two clear cases of triple eruptions, both occurring after a reinjection of serum. In one case the eruptions appeared on the first, third and seventh days and in the second case they occurred on the second, seventh and tenth days following the reinjection.

Axenow,^(c) also, reports eruptions occurring in three and even four distinct periods, following the injection of large amounts of Moser's "scarlet fever serum." Of the 683 cases presenting symptoms of serum allergy, 10 per cent. suffered a triple eruption and 2.3 per cent. a quadruple eruption.

As has already been said, the recurrent eruption appears to be due to the presence, in the injected whole horse serum, of more than

* See page 159.

References: (a) 110. (b) 117, 68, 121, pp. 95 and 107; 208, p. 575; 224. (c) 26.

the chemically defined substance. This is indicated by the fact that, whereas, of those exhibiting serum allergy following a single ordinary injection of whole serum, about 6 per cent. present a recurrent eruption, not a single instance of recurrent eruption occurred in 129 cases of allergy caused by the injection (in some instances repeated) of the isolated pseudoglobulin of horse serum. The "double reaction" of serum allergy would seem, thus, to be the clinical expression of a double allergy to two chemically different allergens in the serum, the reactions to which may be synchronous, overlapping or separated by an interval of time.

The triple reactions of Goodall, as well as the triple and quadruple reactions of Axenow, are susceptible of a similar explanation.

There is, finally, to be considered the third point of clinical evidence presented by von Pirquet and Schick in support of their theory, namely, the local edema, which they look upon as a specific phenomenon—one due to the local reaction of specific antibodies and the reinjected antigen. This hypothesis should limit the occurrence of the phenomenon to a second or further injection. However, the authors report an instance of local edema occurring after a first injection. Von Pirquet and Schick explain this instance as due to the large quantity of serum which was injected; they recognize as "specific edema" only that occurring after the injection of small amounts of serum (1-10 c.c.). On the other hand, they admit that in numerous cases the local reaction following a reinjection of this small quantity cannot be distinguished from that caused by a first injection of a like amount. In one of their cases necrosis occurred about the point of reinjection of the serum. Local edema does not always occur at the reinjection of serum, even in those that are subject to the other expressions of serum allergy.

These local phenomena of serum allergy, also, find their analogies in the allergic effects of drugs at the site of their injection, in ordinarily non-toxic dose. Here, too, have been noted local edema and necrosis as a part of the expression of allergy to the drug.

Beside the several already enumerated inconsistencies that make the clinical phenomena of serum allergy uncomfortable to the antibody-antigen theory of von Pirquet and Schick, there is other clinical evidence, much of which has been referred to, that must offer serious difficulty to any such theory. This evidence is found in the following remarkable parallelism exhibited by the phenomena of drug allergy and those of serum allergy:

(1) The most common symptoms of both are fever and eruption and these symptoms are indistinguishable in the two conditions in any respect.

(a) In both conditions the fever and the eruption are coordinated symptoms, and they often occur independently of each other.

(b) The fever in both may reach a high point (106° F. or higher).

(c) The eruption in both is polymorphous, the common forms in both being identical.

(d) Itching is a prominent characteristic of the urticarial eruption in both conditions.

(2) Edema is present in both drug and serum allergy.

(3) Joint pains are present in both, though, according to the records, more frequently in serum allergy than in drug allergy.

(4) Mucous membranes are seldom, if ever, affected in either condition.

(5) Leukopenia has been observed in both.

(6) The blood-pressure has been found to be lowered in the few cases of drug allergy in which this aspect was studied and also in one case of serum allergy reported by Weil.^(a)

(7) Local edema and necrosis has been observed in both conditions at the site of injection, though more commonly in serum allergy.

(8) A variable incubation period has been noted in both conditions and in both a shortening of that period has been observed after a reinjection, more commonly, however, in serum allergy.

(9) Recurrent symptoms have not been reported in drug allergy as they have in serum allergy. This difference is in accord with the explanation of the recurrent symptoms of serum allergy that is offered above.

(10) The specificity of serum allergy has been assumed without experimental evidence; that of drug allergy has been thoroughly established.

The fact, that, in the great majority of cases of serum allergy, the symptoms follow the serum injection after a period of incubation, may be urged in favor of an immunological mechanism in this condition. However, this argument can only be rejected when it has been tested with the question, Is the incubation period of an allergy evidence of an underlying immunological process? The answer to this question has already been provided in the discussion of drug allergy in which were cited the numerous recorded instances of allergic symptoms developing between 5 and 21 days after a single administration of a *non-antigenic drug*.

The differences between the drug and serum allergies, as presented in the preceding comparison, are chiefly of a quantitative nature and they are, perhaps, dependent upon the proteid or colloid property of the serum allergens as distinguished from the crystalloid character of the drug allergens.

However, *serum allergy exhibits no peculiarity that can serve as a criterion of separation of this condition from that of drug allergy and there is, thus, no occasion offered by the manifestations of serum allergy to seek an underlying mechanism that would be different from that operative in drug allergy, that is, one dependent on an antibody-antigen reaction.*

A prominent feature of the data contained in the reports of the various observers of serum allergy is the often wide difference in the character of the condition in important respects as exhibited in the

different reported series. This difference is particularly apparent in the percentage of incidence and the incubation period.

It is, therefore, in place to suggest that, in formulating some of their important conclusions, von Pirquet and Schick were unduly influenced by fortuitous combinations of circumstances as they occurred in the series of cases that came under their observation.

Reference has been made to instances of insensitiveness brought about, in drug allergy, by the successive administration of small doses of the drug in a manner simulating the process of desensitization in anaphylaxis. If serum allergy is a condition whose etiology is identical with that of drug allergy, it should be expected that under the conditions just mentioned the phenomenon of induced insensitiveness would be encountered also, in serum allergy. Actually, instances are not uncommon in which a first administration of serum has produced the characteristic symptoms of allergy, whereas subsequent injections were not followed by any symptoms. However, such instances have not been reported to occur under the conditions usual in the establishment of either of the two forms of specific antianaphylaxis, that is, desensitization or antianaphylaxis by antibody protection.

An important characteristic of the process of desensitization is the regularity with which it operates in anaphylaxis. The subcutaneous injection of 0.025 c.c. of serum completely desensitizes actively sensitized guinea pigs. On the other hand, the production of insensitiveness in serum allergy by the repeated injection of small doses of serum has been found, by Friedlander and Runnels,^(a) to be quite beyond control.

These authors, in their report on the reaction following the use of antipneumococcic serum, state that in all cases they gave as many as 5 preliminary "desensitizing" injections of the serum, at intervals of 30 minutes, in amounts that aggregated about 11.5 c.c. This amount corresponds with about 0.05 c.c. of serum for a guinea pig, a quantity which never fails completely to desensitize an actively sensitized animal of that species. The authors specifically state that the last two portions of 4.0 c.c. of serum were administered intravenously. Nevertheless, these preliminary injections did not prevent the development of the symptoms of serum allergy in a number of cases* upon the subsequent intravenous injection of 100 c.c. of the serum—a quantity corresponding with about 0.5 c.c. for a guinea pig. It is important to note that the large injection was made on the same day as were the preliminary small ones and that the resulting symptoms appeared, in all of these instances, so soon (within 48 hours) after the administration of the large therapeutic dose of serum that the possibility of a new formation of antibodies can be excluded.

The absence of the phenomenon of desensitization in serum allergy, as demonstrated by the observations of Friedlander and Runnels, presents a serious difficulty to the anaphylaxis theory of that condition

* At least five (personal communication from Major Friedlander); see, also, cases reported by Grysez and Dupuich (114) and by Netter (169).

Reference: (a) 104.

because, although the successful suppression of a state of hypersensitiveness by preliminary injection of small doses of the agent (as in the cited case of quinin allergy) does not, by any means, prove an antibody-antigen nature of the condition, the failure of such a procedure to remove the hypersensitiveness must obviously indicate that the latter is not due to an antibody-antigen reaction. In this respect the observations of Friedlander and Runnels are the more significant because the desensitizing injections were made at a time when circulating antibodies are never found; that is, under circumstances most favorable to the neutralization of any hypothetical cellular antibodies that might be assumed to be responsible for the symptoms of serum allergy. Weil's ^(a) explanation of the failure of "desensitization" in serum allergy is, thus, not applicable here.

As has been set forth in the section on antianaphylaxis, the repeated injection of the antigen in the preanaphylactic period in the guinea pig regularly produces the state of antianaphylaxis by antibody protection, which can be overcome only by the injection of large amounts of the antigen. The observations of Currie, ^(b) already cited, have proven that the corresponding treatment in human beings does not induce any demonstrable insensitiveness in serum allergy, nor does it, indeed, exert any influence whatever on the course of the symptoms of that condition.

The case of prolonged serum disease reported by Flandin ^(c) appears to be inexplicable by any immunological theory. A woman, having received a subcutaneous injection of diphtheria antitoxin, began, thirteen days later, to have edema and an eruption of purpuric character, which disappeared when the patient went to bed but returned when she got up. After this condition had persisted 15 months it was interrupted by an intradermal injection of 0.1 c.c. of horse serum, which had been given to determine the existence of a sensitization to the serum—the test resulting *negatively*. The condition recurred after a week, but further small injections of horse serum regularly caused a disappearance of the symptoms, which returned several times at increasing intervals and in relatively mild form.

The astonishing observations recently reported by Marie ^(d) deserve special attention. This author describes two instances of urticarial eruption, each following a second intravenous injection of 20-40 c.c. of human serum from typhoid convalescents into typhoid patients. This result would seem certainly not to represent an antibody-antigen reaction, since iso-precipitins had not previously been demonstrated, and anaphylaxis had not been produced with homologous serum. However, the observations of Marie cannot be interpreted in this sense because in both of his cases precipitins could be demonstrated, which, in one case, reacted with several normal human sera as well as with the sera of the two donors. Nevertheless, it would be unjustified, in the face of the great body of adverse evidence that has been presented, to con-

clude that the eruptions, in these instances, were the result of an antibody-antigen reaction.

Prevention of Serum Disease.—Since the symptoms of serum allergy have been universally regarded as an expression of anaphylaxis, the prevention of those symptoms has, naturally, been one of the problems that have occupied the investigators of anaphylaxis as well as the clinicians and this object has been pursued in two directions.

On the one hand, the attempt was made to remove the allergens from antitoxic sera or to reduce their amount in the therapeutic dose of antitoxin without causing a corresponding loss of antitoxic antibodies, these efforts resulting in the methods of concentration, one of which—the Atkinson-Gibson method—is in general use in the preparation of antitoxin. Many of the studies of the properties of the anaphylactogens, also, were pursued with a similar object more or less frankly in view.

On the other hand, the prevention of the symptoms of serum allergy has been sought with the procedure employed in the desensitization of sensitized guinea pigs, that is, with the preliminary injection of a relatively small quantity of serum.

The concentration of antitoxin by the method of Atkinson-Gibson, that is, by the elimination of all of the protein components of the serum excepting the pseudo-globulin, which carries the antitoxic principle, has not prevented the development of serum disease following the therapeutic use of the antitoxin. However, the observations of Park and Throne ^(a) on a series of 100 cases of diphtheria, half of which received injections of whole antitoxic serum, the other half receiving injections of the pseudo-globulin fraction alone, seem to indicate that the allergic symptoms produced by the latter preparation are considerably milder than those caused by whole serum. The comparison of the effects in the two groups of cases was made the more valid by the fact that the pseudo-globulin preparation employed was derived from the same mixture of antitoxic sera which was used for the "whole serum" injections.

The authors noted, also, that the eruption usually persisted for a longer average time after the injection of whole serum than it did after the administration of the pseudo-globulin alone. Both urticaria and erythema were noted in both groups.

In a statistical review of a consecutive series of 1519 cases injected with the Atkinson-Gibson preparation the writer's attention was drawn to the absence of recurrent eruptions in all of the 129 cases that presented symptoms of serum allergy. Recurrences of eruption were lacking, also, among the 23 cases of the series of Park and Throne that received the pseudoglobulin, although three of the 36 children that presented allergic symptoms after injections of whole serum suffered such recurrences. This point of difference in the allergic effects of whole serum and those of the pseudo-globulin fraction has already been discussed.*

The application of the procedure of "desensitization" has, also,

* This volume, pages 168 and 173.

Reference: (a) 189.

VOL. I.—12.

failed to accomplish its object in the prevention of the symptoms of the usual form of serum allergy. The illuminating observations of Friedlander and Runnels, which demonstrate this failure, have already been discussed.^(a) However, it is not so much the avoidance of the ordinary clinical expressions of serum allergy, as it is the prevention of the rare fatal form of "reaction" to the administration of anti-toxic sera, which is sought with the procedure of desensitization.

As has been pointed out,* the deaths that have been reported to have followed immediately the injection of serum, have, with few exceptions, occurred after a first injection. In one of these instances, the quantity of serum injected was small (500 units of antitoxin, that is, 0.5 to 1.0 c.c.) and the injection was made by the subcutaneous route. In a case, reported by Kerley,^(b) of a boy clinically hypersensitive to horse (among other things), injections, at two-week intervals, small amounts of horse serum were given, the first dose being of one-half minim (about .025 c.c.). This dose was gradually increased until, finally, upon 4 minims being injected at one time, an alarming shock resulted. Hence it is evident that if the prevention of such accidents is to be attempted by the method of desensitization, the preliminary dose of serum must be considerably less than 0.5 c.c. Nevertheless, the writer is informed that it is the practice of some to give a "desensitizing" injection of as much as 1.0 c.c. of serum a short time previous to the administration of the larger therapeutic dose.

Actually, there is no clear record of a fatal issue in serum allergy having been prevented with the procedure of desensitization, and it would seem, therefore, unjustifiable to depend upon an arbitrary application of the principle of that procedure, such as the practice just referred to, for the prevention of such accidents.

The first step in the rational treatment of a case such as those we are considering must be the diagnosis of the existing fatal hypersensitiveness, and for this purpose there are two kinds of evidence: First, such individuals are often known to be subject to attacks of "hay-fever" or asthma when in the neighborhood of horses; and secondly, the hypersensitiveness can be demonstrated by the intracutaneous application of a minute quantity of horse serum (by injection or through an abrasion), the condition being evidenced by the immediate formation of a wheal-like swelling extending some distance from the point of application of the serum.**

If the administration of a therapeutic serum appears urgently indicated in such an individual, test injections should be given at 30-minute intervals by the intramuscular or deep subcutaneous route and the dose should be cautiously increased, by not more than 0.1 c.c. at each successive injection, from an initial dose of, at most, 0.1 c.c. until symptoms are exhibited. Thereafter, it would seem safe to try half-hourly injections of, perhaps, somewhat less than the largest amount that

* See page 135.

** See chapter on Hay-fever in this work.

References: (a) 104. (b) 129.

had caused no symptoms, upon the assumption that the development of symptoms is not dependent on the sum of all of the doses administered, but upon the amount injected at one time.

Hay-fever.—Hay-fever is a characteristic symptom-complex that depends, not upon the influence of a specific agent, as do the infectious diseases, but entirely upon an inherited predisposition on the part of the respiratory and conjunctival mucous membrane.

The clinical aspect of this condition need not be discussed here, since that aspect is treated in detail elsewhere in this work. However, it may be pointed out that the symptoms of hay-fever are not only local but general. It is, therefore, not correct ^(a) to define hay-fever, as Cooke, Flood and Coca ^(b) have done, as a clinical expression of a local hypersensitiveness; indeed, the existence of the general reactivity of hay-fever subjects is an important connecting link between this condition and the other forms of allergy (serum, drug, food).

The agents first to be recognized as an exciting cause of hay-fever were the pollens. Blackley, ^(c) in the monograph in which he presented convincing evidence of the etiological relationship of pollen to seasonal hay-fever, referred to the "odor given by certain animals" as a "supposed cause of a form of hay-asthma"; but he explained such attacks as possibly due to pollen carried in the fur of those animals. ^(d)

Dunbar, ^(e) whose researches finally forced the acceptance of Blackley's experimentally founded theory, entertains the belief, which is still favored by some, ^(f) that the active principle in pollen which produces the symptoms is a toxin. The chief difficulty involved in the toxin theory of hay-fever "lies in the fact that, to the great majority of individuals, as many as a thousand times the amount of the pollen extracts that is 'toxic' for the hay-fever patient is entirely innocuous." ^(g) Such a non-susceptibility of normal individuals, as Cooke and Vander Veer ^(h) have pointed out, in order to be considered comparable with the natural human immunity to diphtheria, would require the demonstration of an antitoxin to the active substance in pollen. However, no such antitoxin has been found in the blood of normal human individuals.

Furthermore, in order to identify the active substance of pollen as a toxin, it is necessary to demonstrate antitoxin formation when the substance is injected into animals. "This requirement is claimed, by Dunbar, to have been fulfilled for grass-pollen by his patented preparation, 'Pollantin.' However, Dunbar's claim in this respect has been refuted by Wolff-Eisner, ⁽ⁱ⁾ who discussed two main objections to it. These were: first, that the curve of saturation of pollen extract and 'Pollantin,' as plotted by Dunbar's assistant, Prausnitz, ^(j) is completely out of harmony with the law of multiple proportions, which governs the neutralization of all known toxins and their specific antitoxins; and secondly, that the alleged antitoxin of Dunbar is toxic to hay-fever patients when injected subcutaneously. To these may be added a third objection, namely, that normal sera of cattle, as Weichardt

References: (a) 221, 227. (b) 61. (c) 41. (d) 41, pp 101-102. (e) 87. (f) 267, p. 138. (g) 61, p. 218. (h) 62, p. 203. (i) 275. (j) 97.

showed, have a therapeutic effect at least equal to that of 'Pollantin.' "

If further argument against the toxin theory of hay-fever be needed, it may be recalled that the typical symptoms of that condition are now known to be produced, in some individuals, by the emanations from certain animals and from non-antigenic substances, such as peptone and tuberculin,^(a) none of which agents can be assumed to be a toxin.

Under the influence of the newly founded conception of anaphylaxis, Wolff-Eisner^(b) applied the principle of anaphylactic sensitization to the explanation of the etiology of hay-fever, the details of this application being similar to the familiar ones of that author's view of the mechanism of anaphylaxis, according to which the antibody-antigen reaction, occurring *in vivo*, liberates a preformed poisonous substance in the antigen, which causes the symptoms of anaphylactic shock. Wolff-Eisner assumes that, as a result of the absorption of pollen-protein through the mucous membranes, a sensitization to that protein occurs; that is, the fluids of the body acquire the faculty of acting upon the protein aggregates (granules) in such a way as to liberate the preformed poisons just referred to.

It is evident that an acceptance of Wolff-Eisner's conception of the mechanism of the anaphylaxis reaction is not necessary to an adoption of the main principle of anaphylactic sensitization, which he proposed in explanation of the phenomenon of hay-fever and, actually, this basic idea has attained a general recognition among writers of various opinion as to the nature and site of the anaphylaxis reaction.

Wolff-Eisner does not comment on the difficulty offered to his theory by the fact that so few human individuals (10 per cent. in the United States, according to Cooke and Vander Veer) become "sensitized." This difficulty is deepened by the observations of Cooke^(c) and of Clowes^(d) that subcutaneous injection into a hay-fever subject, of a pollen protein to which the individual is not naturally hypersensitive does not induce clinical hypersensitiveness to that protein. Finally, the theory of Wolff-Eisner is embarrassed by the complete failure of Cooke, Flood and the writer either to demonstrate precipitin or complement-fixing antibodies in rabbits, after repeated injections of a pollen extract, or with that extract to induce, in guinea pigs, a condition of anaphylaxis. Thus, the preparation, though rich in the specific exciting agent of the pollen, appears to have lacked all antigenic functions.

It is not to be inferred, from the latter experiments, that pollen contains no antigenic protein. It seems, indeed, that, with certain methods of extraction, such proteins are regularly obtained and the concentration of these proteins, as determined with immunological reactions, is wrongly regarded, by some,^(e) as an index of the concentration, in the different preparations, of the true exciting agents of hay-fever, which, as has been said, appear to lack antigenic properties.

In order to explain, on the basis of a theory of protein sensitization,

References: (a) 76, p. 1124. (See also article by R. A. Cooke in this work.) (b) 275, p. 119. (c) Personal communication. (d) 57. (e) 56.

the striking fact that so small a proportion of human beings are subject to hay-fever, it is necessary to assume a peculiarity of the mucous membranes of such individuals whereby the entrance of pollen proteins into the cell complexes of the body is facilitated or, indeed, made at all possible. However, such an assumption is rendered untenable by the further striking and important fact that the majority of hay-fever subjects (57.7 per cent. of the series reported by Cooke and Vander Veer) are hypersusceptible to only one protein or group of proteins. In other words, it is inconceivable that the mucous membrane of one individual should be so altered as to permit the absorption of only one group of proteins while that of another is abnormally permeable to some other group. Moreover, Cooke and Vander Veer present statistical proof that hay-fever subjects are no more likely to present the symptoms of serum allergy after injections of antitoxic serum than are other individuals. Thus, no general tendency to become hypersensitive to any protein that has passed the natural barriers to the cell-complexes of the body could be shown to exist in the hay-fever subject.

In view of the foregoing considerations, particularly the failure of Cooke and of Clowes artificially to sensitize human beings and the failure of others to sensitize guinea pigs or to produce demonstrable antibodies in rabbits with injections of pollen extracts, it is difficult to interpret the experiments of Ulrich,^(a) who reports success in all of five attempts to induce, in guinea pigs, a hypersusceptibility of the nasal and conjunctival mucous membrane simulating that of hay fever. In similar experiments G. H. Smith^(b) obtained only negative results.

The failure of both the toxin theory and the theory of protein sensitization to explain the etiology of hay-fever is amply compensated for by the recent establishment of the influence of heredity as the sole determining factor in the causation of that condition.

That hereditary influence plays some part in the etiology of pollen allergy has long been recognized. Phoebus^(c) is said to have given this question some consideration. Wynman,^(d) in 1872, wrote: "Of 77 cases recorded in our table, in 15, more than one member of the same family is also affected—a much larger proportion than exists in the community generally." "The probability is that the family predisposition has been rather underrated than overrated." "As the facts now stand, it must be admitted that some families suffer more than others." Beard,^(e) in 1876, found that out of 190 cases studied by him, 66 (35 per cent.) had one or more relatives that were affected with hay-fever. MacKenzie^(f) found as many as 40 per cent. of hay-fever subjects with a family history of hay-fever, while Garel^(g) reported only 20 per cent. with such history.

Finally, Cooke and Vander Veer, assuming the identity of the etiological basis of hay-fever and that of the food idiosyncrasies, the animal idiosyncrasies and the susceptibility to poison ivy, were able, in a study of the family histories of 500 cases of such conditions, to demonstrate

References: (a) 227. (b) 223. (c) 193, inaccessible to the writer. (d) 277. (e) 31. (f) 153. (g) 106.

conclusively the hereditary transmission of the tendency to become hypersensitive to these various proteid substances.

The evidence presented by Cook and Vander Veer in proving this conclusion is drawn from their investigation of the difference in the average age of onset of symptoms and in the incidence of hypersensitiveness in the offspring, according as there was a positive bilateral family history, a positive unilateral family history and the absence of a family history of any of the selected forms of human hypersensitiveness.

First, however, the authors laid down the important principle that the hereditary transmission could not be that of a hypersensitiveness to a particular protein or group of proteins. The form of the hypersensitiveness in the offspring was often different from that in the parent; indeed, when the inheritance was material the form of hypersensitiveness in the child was much more often different from that of the mother than it was identical with it.

The influence of heredity on the age of onset of symptoms of hay-fever was shown in the fact that, in those cases in which a *bilateral* inheritance could be elicited, symptoms began before the fifth year in 36.3 per cent. of the individuals, whereas 14.3 per cent. of the group in which a *unilateral* inheritance could be found and only 5 per cent. of those with *no demonstrable inheritance* began to exhibit symptoms before the fifth year of life. These striking differences in the average age of onset are maintained up to the tenth year of life, the corresponding percentages for this longer period being 66.2, 32 and 17.7.

The considerable number of the cases forming the basis of this analysis appears to justify the acceptance of the authors' conclusion that "*inheritance, therefore, does exert a distinct effect upon the age of onset of symptoms of sensitization (hypersensitiveness); the more complete the inheritance the earlier the manifestation.*"

A comparison of the percentage of individuals, in the three groups of Cooke and Vander Veer's cases, that began to exhibit symptoms after the forty-fifth year of life reveals evidence which confirms the foregoing conclusion. Of those known to carry a double hereditary influence none remain unaffected at this period, all of the members of this group having shown symptoms previous to the fortieth year. Of those in whom a unilateral hereditary influence is demonstrable, only 2 per cent. become affected after the forty-fifth year, whereas, of those in whom the hereditary influence is not discovered in the family history, as many as 5 per cent. have not yet begun to suffer symptoms at that age.

The influence of heredity on the incidence of hypersensitiveness was considered, by Cooke and Vander Veer, from the point of view of the Mendelian laws of inheritance.

Assuming the character of human hypersensitiveness (allergy) to be a dominant, in the sense of Mendel and assuming, further, that, in the cases under observation, this character occurred in the impure condition (that is, mixed with the recessive character of absent hypersensi-

ness), the authors calculated that, when both parents are affected, 75 per cent. of the offspring should be affected and that, when only one parent is affected, 50 per cent. of the offspring should be affected. Actually, under the first-mentioned circumstances, 67.5 per cent. of the offspring, and under the second, 60 per cent. were found presumptively to be affected.

In view of the obvious difficulties attending such an investigation, these results seem, indeed, as Cooke and Vander Veer write, "strongly to suggest that [the tendency to the forms of hypersensitiveness in human beings which they included in their questionnaire] is inherited as a dominant characteristic."

This important conclusion alone would seem obviously to remove the forms of hypersensitiveness referred to from the category of immunological (anaphylactic) phenomena, particularly because one is unable, under the limitations of the facts set forth above, to conceive in what way a faculty of *artificial sensitization* to only one protein can be inherited, as would have to be assumed in the majority of cases of human hypersensitiveness.

Nevertheless, Cooke and Vander Veer adhered to the theory that the forms of human hypersensitiveness which they were considering were due to acquired changes of an immunological character, which, however, they were forced to assume to be "dependent upon some other factor than the mere parenteral injection [introduction] of native heterologous protein."

In a later study, Cooke, Flood and the writer^(*) concluded that, while the various forms of human protein hypersensitiveness (serum disease not being considered) are "established spontaneously and never by immunological process," nevertheless, since the clinical insensitivity resulting from injections of the offending protein recalled that of desensitization in anaphylaxis, these authors assumed the existence, in the sensitive tissues, of antibody-like substances, which were held to be responsible for the "reaction" of the clinical hypersensitiveness. The fallaciousness of the analogy on which this idea rests is sufficiently exposed by the fact that the tolerance attained in hypersensitive human subjects by the injection of the particular protein to which they are sensitive is often far removed from the absolute insensitiveness of the desensitized animal in anaphylaxis. The idea, itself, represents the last vain effort of the theory of protein sensitization to adjust itself to a series of opposing facts.

Through their assumption of a common etiological basis in hay-fever and food idiosyncrasy, Cooke and Vander Veer were led to the important discovery of the sole determining factor of heredity, which underlies both of these conditions. However, as we have seen, the theory on which that assumption was founded, namely, that both of these forms of allergy are the result of a protein sensitization, appears, at least as far as it concerns hay-fever, to be untenable. In fact, the clear demonstration, by these investigators, of the operation of the factor of heredity

Reference: (a) 61.

in these two forms of allergy renders superfluous, also, the assumption of an anaphylactic nature of food idiosyncrasy.

Such assumption has to rest, first, upon the mere fact that the food-stuffs that have been observed to excite the characteristic symptoms of idiosyncrasy contain proteins and secondly, upon a single unconvincing experiment by Bruck ^(a) in the production of passive anaphylaxis to pig's serum by the injection, into two guinea pigs, of the serum of an individual who was subject to pork idiosyncrasy.

The presence of proteins in foodstuffs is not sufficient even to prove that those proteins are the actual exciting agents concerned in food allergy (though this seems probable), much less to prove that the exciting agents themselves are always antigens. Of possible significance in this connection is the failure of Volk ^(b) to demonstrate antigenic property in the substances of the strawberry that excite the symptoms of allergy to that fruit.

The purpose of Bruck's experiment was to demonstrate specific anti-pig antibodies in the blood of the affected individual. However, it is important to bear in mind that, even if antibodies could be conclusively demonstrated in the blood of the subjects of food allergy, this fact, as was pointed out in the discussion of serum allergy, could not, of itself, prove the participation of the demonstrated antibodies in the production of the allergic symptoms.

The anaphylaxis theory of food allergy, like that of pollen allergy, has suggested the application of the procedure of desensitization to the treatment of the former condition and the tolerance attained, in many cases, as a result of such treatment has tended to confirm the impression of an immunological basis. However, the same degree of clinical insensitiveness has recently been found to be obtainable, in one case, by the administration one hour before meals, of 0.5 gram of peptone ^(c) and this observation, in itself, would seem to place in doubt the specificity of the effect under consideration. It is true that the phenomenon may be comparable with the exhaustion of the anaphylaxis mechanism in the liver of the sensitized dog, which can be induced, also, with peptone. However, the latter condition in the dog is, apparently, of longer duration than is the relative insensitiveness produced with peptone in the case of food allergy, and, furthermore, the administration of the peptone caused no symptoms in the individual so treated.

The difference in the natural manifestations of hay-fever and of food allergy would seem to discourage any idea of a relationship between these two conditions. In hay-fever it is the mucous membranes that are involved—the gastro-intestinal, occasionally, as well as the conjunctival and respiratory. In food allergy the characteristic symptoms are seen in the gastro-intestinal disturbances and the eruption. Nevertheless, the researches of Cooke and Vander Veer have established the etiological relationship between hay-fever and food allergy and there is, also, evidence which points to a similarity in the physical basis of the two superficially different conditions. This evidence consists in the well-

References: (a) 49. (b) 233. p. 1125. (c) 188.

known fact that the skin of hay-fever subjects is often highly hypersensitive to the intradermal application of the pollen extracts and, also, in the observation of Cooke that in some instances of hay-fever the subcutaneous injection of the extract of the pollen to which the individual is hypersensitive, results in a general eruption. The hypersensitiveness in hay-fever is, thus, not confined to the mucous membranes but it may be shared by the skin, with which, however, under natural conditions, the active agents of the pollens do not come in contact in amount sufficient nor in the state of solution necessary for the production of the characteristic lesion of allergy in that organ, namely, the eruption.

The close similarity in the manifestations of drug and serum allergy has been set forth in detail and the similarity in the phenomena and the etiological bases of food allergy and of hay-fever has been shown. There are, furthermore, clinical features common to these two pairs of conditions, as well as other considerations which warrant the suggestion of a common etiology and mechanism in all of them.

The hypersensitiveness of the skin has been demonstrated in all four conditions. Edema is produced, under some circumstances, in all, this feature being seen in food allergy and also, sometimes, after the injection of pollen extract into hay-fever subjects. Fever has been observed in all of these conditions, though this symptom is relatively infrequent in hay-fever, perhaps because of the minute amount of the exciting agents that gains access to the circulation. A fall of blood-pressure and a leukopenia occurs in drug and serum allergy as well as in food allergy.^(a) These two features have not been looked for in hay-fever.

We have associated the conditions that we are discussing on the negative ground that an antibody-antigen mechanism had not been demonstrated in the causation of any of them, and the evidence at hand makes it appear, indeed, unlikely that such a mechanism is operative even in those allergies in which the exciting agents possess a protein nature. However, the researches of Cooke and Vander Veer have disclosed a positive basis of association, which if it is extended to include both drug allergy and serum allergy, will not only completely justify the association itself on the ground of a common etiology, but will confirm the separation of the phenomena of allergy from those of anaphylaxis.

TUBERCULIN SENSITIVENESS

(Tuberculin Reaction)

Among the clinical manifestations of human pathology that have been placed by some in the category of anaphylactic phenomena, that is, of phenomena due to an interaction of antigen and specifically related antibody, stands prominently the "tuberculin reaction."

The discussion of the nature of the tuberculin reaction will be facilitated by pointing out at once that this reaction, which was shown by

Koch and others to be dependent upon an existing infection with the tubercle bacillus, is different from the allergic effects* of tuberculin, which may be exhibited by individuals that are not subjects of an active tubercular infection.

The tuberculin reaction was originally elicited by Koch by subcutaneous injection and this route of administration is still preferred by some^(a) on account of the information obtained by its use as to the location of the tuberculous lesions ("focal reaction"). It was found later that local reactions of similar import could be elicited with other modes of administration. Thus, a "tuberculin reaction" of diagnostic significance is obtainable by cutaneous application (von Pirquet^(b)); by percutaneous application (Moro^(c)); by intracutaneous injection (Mendel-Mantoux^(d)) and by introduction into the conjunctival sac (Wolff-Eisner;^(e) Calmette^(f)).

The tuberculin reaction is specific, in the sense that the tissues of the tuberculous individual are sensitive only to the products of the tubercle bacillus.

The dependence of the tuberculin reaction upon the presence of a tubercular infection had been demonstrated by Koch in his original experiments with guinea pigs. The later controls, as conducted by autopsies on many thousands of tested human individuals, have revealed discrepancies of less than 3 per cent. between the autopsy findings and the results of the test.^(g)

The material used in the production of the tuberculin reaction possesses no primary toxicity in many times the amounts usually employed in the subcutaneous test (0.0002 to 0.01 c.c.). One c.c. of pure tuberculin has been injected subcutaneously into a baby without causing the least symptoms.

The properties of the specific active principle in tuberculin were studied by Koch, who found that it differed from the native proteins in its resistance to heat (120° C. for several hours) and its diffusibility through a dialysing membrane; and that it differed from the peptones in that it could be precipitated with acetic acetate. Kühne^(h) excluded the tubercle bacillus on a protein and peptone free culture medium and produced, thus, a tuberculin to which the tuberculous individual reacted as to the tuberculin prepared in the usual way. Loewenstein and Pick,⁽ⁱ⁾ also employing a protein and peptone free medium, produced an active tuberculin which responded negatively to the tests for protein, but in which were substances that could be precipitated with tannic acid and mercuric potassium iodid. The fluid responded positively to the Molisch test for carbohydrate. The active substance was completely removable by dialysis, and it could be destroyed with pepsin or trypsin digestion. According to Loewenstein^(j) the protein free tuberculin is somewhat

* See page 180.

References: (a) 146, p. 561. (b) 239. (c) 164. (d) 154, 159. (e) 276. (f) 53. (g) 93. (h) 137. (i) 148. (j) 146.

less active in its local effect and much less active in its general effect than the original preparation of Koch.

It may be pointed out here that the demonstrated non-protein nature of the active constituent of tuberculin makes it a priori unlikely that it possesses anaphylactogenic property.

Any adequate theory of the mechanism of the tuberculin reaction must provide explanation of the following established facts concerning the reaction:

(1) The reaction appears not at once upon the application of the tuberculin but after an incubation period of 16 hours or longer.

(2) The reaction is absent in the last stages of tuberculosis.

(3) A positive reaction becomes negative just after the appearance of the eruption of measles [and during the attack of pertussis.—EDITOR].

(4) A positive reaction becomes negative after a course of tuberculin therapy.

(5) A reinjection of tuberculin into a tubercular individual may cause a reaction at the site or sites of previous injection.

(6) A reinjection may cause an intensified and accelerated reaction especially if the reinjection is made at the site of a previous injection.

(7) The tuberculin reaction, as induced with the subcutaneous injection, is not only "local" (at the site of injection) and general (fever, etc.) but also "focal" (about the tubercular lesions, wherever they may be situated).

The first to assume an antibody-antigen reaction as the underlying cause of the tuberculin reaction were von Pirquet and Schick,^(a) who believed that the combination of antigen and antibody resulted in the formation of a toxic product. With the further development of the study of anaphylaxis this idea has survived in some places in spite of the numerous difficulties that are attached to it.

The search for antibodies in tuberculous human individuals has been, for the greater part, but meagerly rewarded. Agglutinins have been rarely found, precipitins not at all; bacteriotropins are slightly if at all increased in tubercular persons. Complement-fixing antibodies, on the other hand, are regularly found. With the observance of certain important technical requirements that have recently been discovered by Miss M. A. Wilson^(b) and by H. von Wedel,^(c) these antibodies appear, actually, to be demonstrable in a high percentage of cases of active tuberculosis.

It should be borne in mind that all of these antibodies are related to the protein constituents of the tubercle bacillus, which are probably different from the active principle of tuberculin.

Indication that the agglutinins are not concerned in the tuberculin reaction is presented by the fact that, whereas the tuberculin reaction diminishes or disappears after a course of tuberculin therapy in human beings, agglutinins may appear for the first time after such treatment.^(d)

A similar lack of relation between the complement-fixing antibodies and the tuberculin reaction in guinea pigs is demonstrated by the ex-

periments of Christian and Rosenblatt,^(a) which were confirmed by Schenk,^(b) showing that those antibodies are not present in the tuberculous animals although the latter are very susceptible to tuberculin. Furthermore, such antibodies are not formed by the normal animal after injections of killed tubercle bacilli; but they can be induced by such injections when these are made into tuberculous guinea pigs.

In the serum of tuberculous individuals that have been rendered insensitive to injections of tuberculin has been demonstrated a power of neutralizing the active principle of tuberculin.^(c) Such a property, Doerr remarks,^(d) has not been seen in anaphylaxis. However, this phenomenon could be considered as analogous to antianaphylaxis by antibody protection.

Sensitizing antibodies have been sought in the serum of tuberculous individuals by means of the technic of passive transfer. Against a long series of negative experiments^(e) of this kind stand a few positive results.

Those of Yamanouchi,^(f) who used rabbits, have been referred by Roepke and Busch,^(g) who failed in 17 trials to confirm Yamanouchi's results, to a possible carboic acid content of the old preparation of tuberculin employed by Yamanouchi.

Helmholz^(h) obtained a local reaction with the dermal test in normal guinea pigs 4 to 6 days after the injection of 4 to 5 c.c. of the serum of tuberculous guinea pigs and he reports a similar reaction obtained in a normal guinea pig 4 days after it had been united to a tuberculous guinea pig by an operation that established an open communication between the two peritoneal cavities. These experiments have not been repeated.

Austrian⁽ⁱ⁾ injected 5 to 10 c.c. of the whole citrated blood of a tuberculous human individual intraperitoneally into 11 normal guinea pigs of 240 to 590 grams weight and, 2 days later, tested the sensitiveness of these animals to an aqueous extract of tubercle bacilli by intravenous injection. Two of the eleven animals died after the intravenous injection with symptoms of acute anaphylaxis, the autopsy findings being typical of that condition. In a later series of experiments Austrian and Fried^(j) were able to make a similar transfer in one case, the result being negative in 24 other cases.

Austrian's experiments cannot be accepted as bearing on the question of the "tuberculin reaction," not only because his tests were made, not with tuberculin, but with tuberculo-protein, but particularly, also, because the reactions which he obtained were like those of acute anaphylaxis and not like those of the tuberculin reaction.

An antibody-antigen nature of the tuberculin reaction is rendered improbable by the experiments of Bail^(k) in the passive transfer of tuberculin sensitiveness in guinea pigs. This was accomplished by Bail by the injection of emulsified tuberculous tissue from the spleen, liver and lymph-nodes of infected guinea pigs into the peritoneal cavity of

References: (a) 55. (b) 208. (c) 194. (d) 76, p. 1112. (e) 76, p. 1111. (f) 278. (g) 202. (h) 118. (i) 24. (j) 25. (k) 28, 29.

normal guinea pigs. With the observance of certain important conditions, Bail's method of transference was uniformly successful. However, the passive transfer failed altogether in the one instance in which the serum (11.0 c.c.) of two tuberculous guinea pigs was injected into a single normal guinea pig.

Bail's method consists in forcing the tuberculous organs, which must contain a great preponderance of tuberculous tissue (tubercles), through a fine-meshed wire gauze and injecting 4 to 6 c.c. of the resulting emulsion into the peritoneal cavity of young guinea pigs. After a period of 6 to 72 hours the test injection of tuberculin is made by any of the usual routes (peritoneal, venous or subcutaneous).

The tuberculin sensitiveness was evidenced, in Bail's experiments, by a resulting local edema (after subcutaneous injection), a focal inflammatory reaction affecting the tissues adjacent to the injected tuberculous material and constitutional symptoms, which always ended in the death of the animal. The symptoms did not begin for an hour or more after the injection of the tuberculin and death did not follow till after 10 to 24 hours or longer.

Bail's results were confirmed by Onaka,^(a) who noted a fall of temperature as a constant characteristic of a successful transfer. The failure of Joseph,^(b) Kraus, Loewenstein and Volk^(c) and others is explained by Bail as due to technical error, especially in the choice of tissue for the transference. Bail shows that it is the tissues of the tubercle and not the organ tissues of the tubercular animal that carry the tuberculin sensitiveness. He believes that the union of the tuberculin with the tuberculous tissues results in the formation of a poison which produces both the focal and the general symptoms. However, this explanation does not seem to reach the local reaction, which is exhibited at the site of injection of the tuberculin when this is made subcutaneously.

The character of the histological changes that take place at the site of the local tuberculin reaction is not without significance with respect to the question of its anaphylactic nature. It appears that in some of those lesions that were subjected to microscopical study the changes resembled^(d) those of tuberculosis, while in others those changes could not be distinguished from the typical changes^(e) of that disease. The pathology of the local tuberculin reaction appears, thus, to be that of tuberculosis, and this specific character of the reaction tissue may have some relation to the instances of a "lighting up" of the reaction at the sites of previous injections after a subsequent one. Such a reaction is conceivably due to a mechanism similar to that which underlies the "focal reaction."

Loewenstein and Rappaport,^(f) observing that repeated small injections of tuberculin caused an increased tuberculin sensitiveness in tubercular individuals, suggested that this sensitiveness is of the same nature as toxin-hypersensitiveness. Two difficulties are attached to this idea:

References: (a) 186. (b) 127. (c) 133. (d) 30. (e) 65. (f) 149.

first, the symptoms of toxin-hypersensitiveness are those of the toxin itself, whereas with tuberculin there is no primary toxicity with which the symptoms of the sensitiveness can be compared; *secondly*, tuberculin sensitiveness cannot, like toxin-hypersensitiveness, be induced in a normal animal, but only in a tubercular animal.

The insensitiveness of individuals in the last stage of tuberculosis need not indicate an absence of the underlying mechanism of the tuberculin reaction in such cases; this phenomenon may be due to a non-specific insensitiveness of the tissues to various toxic influences. This suggestion is drawn from the experiments of Kraus, Loewenstein and Volk,^(a) who found that "cachectic" guinea pigs, which were insensitive to tuberculin, were also insensitive to intracutaneous injections of diphtheria toxin (1:2000).

The nature of the tuberculin reaction remains unknown. That it is probably not an expression of anaphylaxis is apparent from almost all of the recorded clinical and experimental facts concerning it. The main difficulties in the anaphylaxis theory of the reaction may be recapitulated as follows:

(1) The active principle of tuberculin is, unlike all the known anaphylactogens, a biuret-free, dialysable substance resembling the polypeptids in its behavior to the digestive ferments and to chemical reagents.

(2) Normal guinea pigs can be sensitized to tuberculo-protein so that the intravenous injection of this material kills the animals in anaphylactic shock. In such animals, however, the tuberculin reaction cannot be elicited.

(3) Tuberculous guinea pigs do not respond with anaphylactic shock when injected with tuberculo-protein or tuberculin, although the latter material, in small doses, produces in such animals a fatal tuberculin reaction.

(4) Passive transfer of tuberculin-sensitiveness with the blood of a tuberculous animal has not yet been convincingly accomplished.

(5) Finally, it appears that tuberculin sensitiveness can be transferred to a normal guinea pig with an emulsion of tuberculous tissue. Anaphylactic sensitization, on the other hand, although resident in the tissues, cannot be passively transferred through injection of an emulsion of such tissues.

Tuberculin Allergy.—It is remarkable that in their discussion of the subject of tuberculin reactions nearly all of the writers omit all reference to the exceptional instances in which the administration of tuberculin gives rise to a characteristic symptom-complex of allergy.^(b) Tuberculin allergy has been encountered in three forms: the dermal (in which the common eruptions have been seen), the mucous (hay-fever^(c)) and the general^(d) (coughing, precordial oppression, accelerated respiration, collapse). The condition is distinguishable from the "tuberculin reaction" of tuberculosis in its characteristic manifestations, its

References: (a) 133. (b) 143, pp. 390-394. (c) Weichardt, cited by Doerry, 76, d) 145.

rarity and its occurrence in non-tubercular individuals. It may be induced with small amounts of tuberculin (0.0002 to 0.0003 c.c.) and, as in drug-allergy, often appears only after repeated administration.

TOXIN HYPERSENSITIVENESS

Repeated injections of sublethal quantities of either diphtheria or tetanus toxin may induce, instead of the usual immunity, a state of marked specific hypersensitiveness^(a) to those toxins, 1, 700 of a normal minimal lethal dose being often enough to cause the death of the animal.

While this condition has been observed in a number of animals, it appears to be most easily and regularly induced in the guinea pig by the repeated injection of sublethal amounts of toxin at short intervals. Attempts to demonstrate the development of hypersensitiveness after a single injection of toxin have not led to uniform results. While hypersensitiveness was shown to follow, in not less than 20 days, a single injection of tetanus toxin,^(b) such a condition, as clearly distinguished from a mere summation effect, could not be induced with a single injection of diphtheria toxin or ricin.^(c) The hypersensitiveness may exist in spite of the coincident development of antitoxic antibodies, which may be demonstrated in the blood. That the condition does not represent a summation effect is proved by the fact that it can be induced by the spaced injection of quantities of the toxin that together are less than a single minimal lethal dose.^(d) That the phenomenon is not mediated by antitoxin is proved, not alone by the fact that the hypersensitiveness is not passively transferable, but also in the fact that guinea pigs which have received injections of diphtheria toxin after the latter has been completely detoxicated with ultraviolet rays^(e) (40 hours' treatment) become hypersensitive to untreated diphtheria toxin, although the detoxicated toxin is incapable of inducing the production of antitoxin in animals. This conclusion must apply, furthermore, against a hypothetical mediation of newly formed "sessile" antitoxic receptors,^(f) inasmuch as the susceptible cells in tetanus intoxication, that is, the ganglion cells of the central nervous system, are not concerned in antitoxin production.

Animals dying as a result of toxin hypersensitiveness almost always present the incubation period, symptoms and lesions that are characteristic of the respective toxin.^(g) This fact, in itself, points to an underlying mechanism that is different, on the one hand, from that responsible for any of the allergic phenomena and, on the other hand, from that responsible for the symptoms of anaphylaxis.

The difference between toxin hypersensitiveness and anaphylaxis is made complete by the fact, already mentioned, that the former is not passively transferable. As Doerr says, in summing up the differences between these two phenomena, animals dying in toxin hypersensitiveness are killed by the antigen, sometimes even in spite of the presence of

References: (a) 46, 206, 234, 273. (b) 147. (c) 136. (d) 150. (e) 73. (f) 132, 235.

antitoxin, whereas death in anaphylactic shock is not caused by the antigen alone, which, by itself, may be innocuous, but by the interaction of antigen and antibody, with the production of characteristic symptoms, the symptoms being identical with different antigens.

Notwithstanding the sharp antithesis exhibited by the conditions controlling these two phenomena, attempts have been made, in several directions, to demonstrate the anaphylactic nature of toxin hypersensitiveness.

Since, in every instance of anaphylaxis that has been identified as such by passive transfer, the presence of antibodies of "amboceptor" nature has been demonstrable in the medium of such transfer, it has been reasonably assumed that this type of antibody is required for the establishment of the condition of anaphylaxis. With the idea that conformity to this rule with respect to toxin hypersensitiveness would provide indirect evidence of its anaphylactic nature, the technic of complement-fixation was applied in the examination of the sera of animals immunized with toxins.^(a) With this method it was believed, for a time, that specific antibodies of amboceptor type had been found and these were supposed to be concerned in the causation of toxin hypersensitiveness. However, these complement-fixing substances were subsequently shown to be non-specific^(b) and they are, doubtless, identical with the similarly reacting bodies that appear in the blood of animals after injections of Witte peptone.^(c)

Friedberger's "anaphylatoxin" theory of the mechanism of anaphylactic shock makes no distinction between toxins and non-toxic proteins, inasmuch as he assumes that through the mediation of antitoxins or protein-antibodies the respective antigens are split into toxic products, these being then split into non-toxic products. From the standpoint of this theory Friedberger, Mita and Kumagai^(d) sought to establish the anaphylactic nature of toxin hypersensitiveness by demonstrating "anaphylatoxin" production when minute quantities of toxin in dry form were mixed with normal guinea pig's serum. It seems a sufficient commentary on these experiments to recall the so strongly supported general conclusion that with the technic of anaphylatoxin production no evidence as to the anaphylactic nature of any phenomenon is obtainable.

Arima^(e) employed the direct method of passive transfer and he believed that the acutely toxic, in a few instances, fatal effect of large injections of toxin into the animals that had previously received injections of antitoxin was an expression of passive anaphylaxis. However, subsequent investigations made it appear likely that the acute symptoms elicited by Arima were due to the carbolic acid content of his toxin preparation.

The recorded facts regarding toxin hypersensitiveness leave us entirely in ignorance of the mechanism of its causation, yet they mark clearly its difference from either anaphylaxis or any of the known forms of allergy.

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CHAPTER VII

INFECTION AND IMMUNITY

BY HERBERT K. DETWEILER, M.D.

- Infection, p. 199—Phenomena of infection, p. 199—The path of infection, p. 202.
- The problem of virulence, p. 207—Toxins, p. 210—Plasmains, p. 211—True toxins, p. 212—Endotoxins, p. 212—Bacterial proteins, p. 212—Method of action of bacterial poisons, p. 213.
- Immunity, p. 214—Natural immunity, p. 214—Ehrlich's side-chain theory, p. 224—Acquired immunity, p. 230.
- Toxin and antitoxin, p. 237—The nature of the toxin-antitoxin reaction, p. 238—Production of antitoxin for therapeutic use, p. 244.
- Agglutinins and precipitins, p. 246—Agglutinins, p. 246—Microscopic agglutination test, p. 247—Macroscopic agglutination test, p. 248—Agglutination tests for the determination of types of pneumococcus, p. 249—Agglutination test for the selection of donors for transfusion of blood, p. 250—Precipitins, p. 254.
- Phagocytosis and opsonic index, p. 259—Phagocytosis, p. 259—Opsonins, p. 260—The opsonic index, p. 262—Practical value of the opsonic index, p. 265.
- Hemolysins, bacteriolysins and other cytotoxic substances, p. 267—The nature of complement, p. 272—Bordet-Gengou phenomenon of complement-fixation, p. 274—Practical applications of the complement-fixation phenomenon—the Wassermann reaction, p. 276—Technic of the Wassermann reaction, p. 278—Problems involved in the standardization of the Wassermann reaction, p. 285—The modification in the strength of the Bordet-Wassermann test during treatment of syphilis, p. 296.

INFECTION

Phenomena of Infection.—When microorganisms gain entrance into the animal or human body, multiply and produce an abnormal condition, or disease, the process is spoken of as infection. The mere presence of microorganisms in the body does not constitute infection. They must be able to reproduce and injure the tissues of the host. It is therefore a progressive phenomenon, and our conception of the condition must be based upon that fact.

The mere presence of organisms in the body, as for example, in the mouth, may be normal. Although the body and all its passages and cavities are sterile at birth, within a few hours the skin and exposed mucous membranes, as well as the entire alimentary canal, become contaminated with many varieties of bacteria, and this condition persists throughout life. It is therefore regarded as normal, although it has been shown, experimentally, that it is not necessary to health. Each

of the various surfaces harbors a more or less constant type of bacteria. Thus the presence of streptococci is to be expected in examining the secretions about the mouth and throat. The colon bacillus is found in the contents of the large bowel; staphylococci are nearly always encountered on the skin surface, and Döderlein's bacillus in the vagina. These organisms lead a saprophytic existence in these locations during health, although many of them are quite capable of producing disease when conditions are favorable.

It is therefore evident that factors other than the mere presence of the microorganism are involved in the production of infection. Granting that a certain organism may be pathogenic, i.e., able to cause disease, it must find a suitable path of entrance into the body, and arriving there, must seek a location in which the environment is conducive to its growth and multiplication. It is well known, for example, that infection with the typhoid bacillus occurs in the great majority of instances, if not in all, by the ingestion of the microorganism with food or drink. Its path of entry is thus by way of the alimentary canal. Staphylococci, on the other hand, usually gain entrance through the skin by way of hair follicles or through an abrasion. Having made their way into the blood or lymph stream, or into the tissue spaces, the invading organism may find itself at once in a favorable environment and begin to multiply and set up an irritation. Such would likely take place in the case of staphylococci, whereas typhoid bacilli would probably locate in the lymphoid tissue and in the gall-bladder. Pneumococci, on the other hand, are dissolved by bile, and therefore could not survive in the gall-bladder, but find extremely favorable conditions in such localities as the lungs, meninges, and serous cavities.

It is not only necessary that the microorganism should gain entrance to a suitable location but even here other factors come in. The defensive mechanism of the host must be reckoned with, as well as the difference in virulence or invading power of the various strains of the same species of bacteria. If the balance of power is in favor of the invader, it may multiply and cause disease by progressively invading more and more of the tissue of the host, or it may spread immediately throughout the body by way of the blood stream, constituting what is called a "septicemia." Some organisms, as the diphtheria bacillus, remain localized, or spread only slightly, but depend for their pathogenicity upon their power to elaborate a specific toxin which is excreted into the blood stream and circulates throughout the entire system, attacking, more or less, all the tissues of the body.

Occasionally two, or even more, organisms may be present in a lesion at the same time. Such a condition is termed a "mixed infection." The recognition of this fact is often important in studying the phenomena of certain cases of infectious diseases. These organisms may gain entrance simultaneously, or one may follow upon the other as a secondary invader. Diphtheria and scarlet fever may coexist. Syphilis and gonorrhea may be contracted at the same time, as may tetanus and gas gangrene. Recently Netter and Salanier,¹ Mathers² and Fitz-

gerald⁴ have reported cases of meningitis in which both the meningococcus and pneumococcus have been isolated from the spinal fluid. Anthrax pustules commonly harbor staphylococci and streptococci as well as the *Bacillus anthracis*. Occasionally the secondary invader entirely replaces the primary infecting organism. There is much evidence to support the view that such is the case in many instances of cholecystitis in which the original streptococcus makes way for the colon bacillus.

In cases of mixed infection, the administration of specific therapy in the form of serum or vaccine should, if possible, cover each organism. In the case of serum, this is not often practicable, as satisfactory sera have not been prepared for many types of organisms, but polyvalent vaccines are much more easily secured, and in cases where vaccine therapy is indicated, observers are agreed that each variety of bacteria involved should be represented in the preparation used.

Bacteria may be conveniently divided into two classes—saprophytes and parasites. The saprophytes are those bacteria which live upon dead organic material. Parasites, on the other hand, thrive best upon the living tissues of the animal organism. A strict classification into these two divisions cannot be made, as many parasites can and do live a saprophytic existence for extended periods of time. Thus, the *Streptococcus viridans* is present in the normal mouth, living upon food particles and debris about the teeth and tonsils, but it has been shown⁴ that these organisms are capable of living a purely parasitic existence, and of causing serious pathologic conditions as a result. The majority of the pathogenic bacteria belong to the class of parasites, but strict saprophytes are often capable of producing disease. Thus organisms of a putrefactive nature may gain entrance into the uterus, in which fragments of placental tissue are retained, and thriving upon this dead matter may elaborate poisons which are the result of their activity in protein cleavage. These poisons are not true toxins produced by the bacterial cell, but are the by-products of putrefaction of the placental tissue. When absorbed into the blood stream they may give rise to serious toxic disturbances. On the other hand, the *Bacillus botulinus* will thrive outside the body, upon dead organic matter, such as canned vegetables, sausages, etc., and elaborate by its cell-activity a true toxin which, upon its ingestion, will cause the most profound intoxication of the subject.

Nor can bacteria be strictly divided into pathogenic and non-pathogenic varieties. Many species are regularly classified as non-pathogenic, and yet have been shown to possess pathogenic power, under certain conditions. Thus Vaughan⁵ has shown that dead cultures of *Bacillus subtilis*, when suitably treated and injected into an animal, can produce toxic symptoms which he ascribes to the toxic portion of the bacterial protein. Thiele and Embleton⁶ claim to have been able to produce granulomata in animals by live cultures of the *Bacillus phlei*. In our laboratory we⁷ have shown that cultures of *Streptococcus viridans* from normal mouths, when injected intravenously into rabbits, may give rise to a variety of lesions, more particularly myocardial and endocardial.

Strict parasites, as for example the gonococcus, are able to grow aside from artificial culture in the laboratory, only upon the animal body itself. When removed from this environment, they may survive for varying lengths of time, but are unable to grow or multiply. Thus it is evident that such bacteria, in order to produce the disease of which they are the cause, must be communicated from person to person directly or almost directly, as in discharges, secretions, epidermal scales, or bites from insects. Infections which require such direct means of transmission for successful inoculation are termed *contagious diseases*. This term, however, is not a satisfactory one, as no hard-and-fast rules can be laid down in its use. It is more preferable to remember that all microbial diseases are *infectious*. Whether they are transmitted directly or indirectly depends upon the viability of the organism outside the body, upon its resistance to heat and cold, light, desiccation, and its cultural characteristics. In cases of chronic bacteremia, in which the organisms may be isolated from the blood over long periods of time, it is not because the bacteria are proliferating in the blood stream, but because they are being thrown out into the circulation from foci situated in the heart valves and other locations in the tissues. It has been demonstrated in our laboratory and in that of Zinsser and others that a bacteremia is difficult or impossible to produce in rabbits, until a suitable focus of infection has been established at some point, from which the bacteria are constantly being supplied into the circulation, where their life is comparatively short. There is much evidence of a clinical nature to support this view. We have seen cases of otitis media with a streptococcal bacteremia, in which the blood became sterile after the focus of infection had been eliminated. Zinsser⁸ mentions similar cases. He also suggests that many cases of chronic bacteremia offer a better prognosis than was formerly supposed. This point was emphasized by Oille, Graham and Detweiler⁹ in cases of chronic bacteremia associated with endocarditis. It follows, therefore, that the blood is more or less antagonistic to the growth of most microorganisms.

The Path of Infection.—As stated before, the path of entrance of bacteria into the body is of great importance in determining the effect upon the host. Certain microorganisms seem to have no power of infectivity when introduced by routes which, with other species, are extremely effective. Thus, when typhoid bacilli are rubbed into the skin, which has previously been scarified, no infection of importance is likely to result, whereas the same organism entering by the alimentary canal gives rise to the infection known clinically as typhoid fever. The anthrax bacillus is very likely to produce a severe reaction whether it is introduced through an abrasion in the skin surface, inhaled into the lung, or swallowed.

In a general way, once any pathogenic organism has gained entrance into the tissues it multiplies and invades the surrounding areas. The tissue fluids, together with the serum and lymph with which the part is bathed, exert an antagonistic action against the invading organism. In this they are assisted by the leukocytes. If the balance of power is

in favor of the host, the growth of the bacteria is inhibited, or completely stopped, those remaining die, and any damage done to the tissues is repaired. If, on the other hand, the balance of power is in favor of the invaders, they may progressively involve larger areas of adjacent structures, or they may gain entrance into the blood stream, producing a *bacteremia*. When a patient is suffering from a *bacteremia* in which the outstanding feature of the clinical picture is the intoxication resulting from the bacterial poisons in the blood, the term *septicemia* is used.

Often a focus, such as an infected wound of the hand, may not succeed in giving rise to a *bacteremia* or *septicemia*, but the organisms may spread by way of the lymph channels. Red streaks up the arm are the clinical evidence of the resulting lymphangitis. Having reached the glands in the axilla, the bacteria are filtered out of the lymph stream, but may succeed in establishing themselves in the gland tissue itself, resulting in a reaction varying in severity according to the virulence of the organism and the resistance of the host, from a slight inflammation with swollen and tender glands, to actual abscess-formation. When the microorganisms, carried by the circulation, gain footholds in various parts of the body, giving rise to metastatic foci of infection with necroses or abscess-formation, the condition is spoken of as *pyemia*.

The path of infection in cases of epidemic cerebrospinal meningitis has been the subject of much study, but so far nothing definite has been proven. The general opinion, however, prevails that the route is by way of the nasal passages, by lymphatics or by the blood stream to the meninges at the base of the brain. Certainly in examining "contacts" for carriers, it is found that the mucous membrane of the nose and throat is the only source from which positive results are obtained.

Having discussed the importance of a consideration of the avenue of infection in a general way, we may now take up systematically the various anatomical structures through which the invading organism may enter.

1. *The skin* and adjacent mucous membranes harbor many bacteria, especially in areas where moisture and warmth are present. From its constant contact with surrounding objects, the skin becomes contaminated with microorganisms from the air, water and soil. Most of these are non-pathogenic, but from the habitual presence of some of them in the minor lesions occurring in the skin—such as stitch-hole abscesses, acne pustules, eczema, etc.—it is held by many observers that they are contributory if not causal agents in their production. Examples of such organisms are *Staphylococcus albus* (epidermidis), *Bacillus subtilis*, *Bacillus zerois*, and other so-called diphtheroid bacilli.

More important than these, however, are microorganisms which find temporary lodgment on the skin, such as *Staphylococcus aureus*, pneumococci, gonococci and the spirochete of syphilis. It is the opinion of the majority of observers that these organisms must gain entrance through abrasions in the skin or mucous membranes and cannot cause infection where the epithelium is intact. We must keep in mind, how-

ever, that the *Staphylococcus aureus* may find a path along a hair follicle, and there is much evidence in supporting the view that the *Spirochæta pallida* is able to produce a chancre where the skin has been unbroken. Certain fungi, as the microsporion and trichophyton, are said to invade the intact superficial epithelium and gradually spread to the deeper structures.

Infection through the skin by the agency of suctorial insects has received much attention, in view of recent researches into the etiology of typhus fever, trench fever and spirochetosis icterohemorrhagica. It has been quite definitely settled that these diseases are louse-borne, and the avenue of infection is the same as in malaria, the plasmodium of which gains entrance through the bite of the *Anopheles* mosquito.

2. The *conjunctiva* harbors such microorganisms as the *Staphylococcus albus* and *Bacillus zerosis* almost constantly, but is usually resistant to infection. The commoner bacteria which may set up an inflammation there are the gonococcus, pneumococcus, bacillus of Morax-Axenfeld, Koch-Weeks bacillus, and *Bacillus diphtheria*.

3. The *tonsils* and *alveolar sockets of the teeth* form excellent atria through which streptococci, particularly, reach the deeper tissues and the blood stream. The tonsillar crypts harbor debris and various types of bacteria, particularly *Streptococcus viridans*. If for any reason the tonsil becomes unhealthy and enlarged, the natural barriers are broken down to a greater or less extent, and the bacteria may invade the tonsillar tissue, either producing a local infection of the tonsil, with pockets of pus, or gaining entrance to the lymphatics and the blood stream, and may give rise to foci of infection in distant parts—as in the endocardium, gall-bladder or kidney.

Similarly, the condition known as pyorrhea alveolaris arises from the lodgment of food particles and bacteria between the tooth and the surrounding tissue. The mechanical separation of these tissues from the neck of the tooth, by careless brushing or more often by neglect, frequently furnishes the first step toward the successful invasion of the tissues by the microorganisms present in the mouth. Sometimes the infection is found at the apex of the tooth, the bacteria having gained entrance by way of a diseased or empty root canal after the infection or death of the pulp. These foci of infection have received much attention in recent years, and are believed by many to be the cause of numerous conditions such as endocarditis, chronic arthritis, nephritis, gastric ulcer, cholecystitis and appendicitis. The striking feature with regard to these dental foci is the comparative insignificance of the lesion in view of the extensive damage it may indirectly cause in other parts of the body.

It is largely due to the work of Billings¹⁰ that the attention of clinicians and laboratory investigators was directed to the importance of tonsillar and dental foci of infection, and their relation to systemic diseases. He calls attention to the researches carried on by himself and his associates in this connection. He finds that foci of infection are responsible for many such general diseases as acute and chronic

rheumatism, gonorrheal arthritis, endocarditis, myositis, myocarditis, septicemia, nephritis, visceral degeneration, thyroiditis, pancreatitis, peptic ulcer, duodenal ulcer and cholecystitis. Rosenow¹¹ believes that various strains of streptococci possess elective affinity for certain structures or tissues, and that, given a focus of infection, the streptococci therein contained, depending on the phase of mutation in pathogenicity, and the affinity of the strain, may produce such systemic metastases as Billings enumerates. His views are supported by various of his pupils, such as Moody,¹² Oftedal,¹³ and Irons.¹⁴

Rosenow's claim as to mutations within the strepto-pneumococcus group have not received general confirmation, and his further statements as to elective localization of streptococci have been seriously questioned by a number of workers. Henrici¹⁵ found that rheumatic lesions in rabbits are produced in equal proportions by both hemolytic and non-hemolytic streptococci, and he does not recognize any strain as specific for rheumatic fever.

Detweiler and Maitland¹⁶ found as the result of numerous experiments that they could not substantiate in full Rosenow's claims as to the elective affinity of these microorganisms. A few strains showed a rather remarkable constancy in location and type of lesion, but these strains were greatly in the minority. The location of the lesions in the inoculated animals seemed to bear no relation to the origin of the streptococci, or to the lesions produced in the patient from whom the strain was isolated.

Hartzell and Henrici¹⁷ call attention to the importance of peridental foci of infection, and their experimental work is of great interest in connection with the relation of such foci to metastatic lesions such as arthritis, myocarditis, etc.

4. Foci of infection may occasionally be detected in the *antrum of Highmore*, and in the *accessory sinuses of the nose*. These foci are sometimes responsible for distant lesions in much the same way as are the dental and tonsillar foci, but their occurrence is not so frequent.

5. The *trachea* and *lungs* form the portal of entry for various organisms, often leading to serious disease. Thus the predilection of the bacillus of Bordet and Gengou, for the tracheal mucous membranes in cases of pertussis, is well known. It is also believed by the majority of observers that the tubercle bacillus, in pulmonary cases, gains entrance through the respiratory tract. It is interesting to note the relation of the trachea and bronchi to the recent epidemic of influenza. While the bacillus of Pfeiffer could not always be isolated, it was found in a large number of cases in the sputum, and in the secretions obtained postmortem from the bronchial mucosa. In view of the almost constant presence of a cough, and of other signs of respiratory infection during the disease, whether pneumonia developed or not, it is likely that the infection is primarily one of the trachea and large bronchi. The fatalities were due to pneumonia. It was unusual to find *Bacillus influenzae* in the lungs in these cases, but pneumococci and streptococci could be demonstrated in nearly every instance. It would therefore

appear that these organisms, present in the mouth and throat as saprophytes, begin to invade the lungs after the soil has been prepared, as it were, by the Pfeiffer bacillus or by some unknown microorganism as a filtrable virus. In other words, they are secondary invaders, becoming parasitic, not because their virulence has been raised, but because of the lowered resistance of the tissues involved, as a result of the damage done by the primary infecting agent.

6. The acidity of the gastric juice renders the infection of the tissues of the stomach more difficult than those of many other organs. This is owing to the antiseptic qualities of the acid. Nevertheless, streptococci are found in the bases of the majority of acute and chronic gastric ulcers, and are presumed by Rosenow²² to be the etiologic factor. These organisms are believed by this observer and by others (notably Billings) to reach this location by way of the blood stream, having gained entrance from foci of infection in the tonsils, teeth, alveolar pockets, or elsewhere. It has been definitely shown, however, that organisms, as for example the tubercle bacillus, may pass from the lumen through the undamaged mucosa of the intestine to the tissues beyond. Typhoid bacilli reach the intestine with food and drink, being apparently able to withstand the action of the gastric juice. From the lumen they pass through the mucous membrane into the blood stream. It is doubtful if these organisms infect in any other way.

Somewhat similar to this is Adami's explanation of the action of *Bacillus coli* in pathologic conditions of the liver and other tissues. He contends that through a mucous membrane damaged by various causes—as excessive use of alcohol—the colon bacilli pass into the portal circulation and are carried to the liver. Here they lodge in endothelial cells in the capillary walls and later throughout the liver cells. Owing to their poor invasive powers, these organisms fail to multiply, and thus they produce no infection, but as they die and undergo digestion, they liberate endotoxin which irritates the surrounding tissues, causing the latter to react by the formation of connective tissue. Such a series of events, in which the main features are the failure of the bacteria to multiply, and the reaction on the part of the tissues to the endotoxin liberated by the disintegration of the microorganisms, is called "sub-infection," a term suggested by Adami.

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THE PROBLEM OF VIRULENCE

The word *pathogenicity* refers to the power of an organism to produce disease. Thus *Staphylococcus pyogenes aureus* is pathogenic for man, inasmuch as it possesses the power to produce abscesses, furuncles and many other forms of infection, including a very fatal form of septicemia. Yet certain strains of *Staphylococcus pyogenes aureus* do not readily produce disease unless conditions are altogether in their favor. Other strains may attack and successfully invade apparently healthy individuals, producing in a short time very serious disease. The great facility with which various strains of the same species may produce disease, while other strains, though pathogenic, lack this facility, makes it necessary to introduce another term—namely, *virulence*. A virulent strain, therefore, is one which possesses the ability to infect readily and severely. A pathogenic organism which has this power in much less degree is said to be of low virulence, and is described as avirulent, or non-virulent.

Not only may different strains vary in virulence, but the same strain may change from time to time in this respect. Cultivation on artificial media often reduces the virulence in a comparatively short time. Sometimes it is necessary to culture the organism in an unfavorable environment. An example of this is shown in Pasteur's method of reducing the virulence of *Bacillus anthracis* by growing it at a low temperature (20° C.). Animal passage, on the other hand, often raises the virulence to a high degree. This, in effect, is what happens during an epidemic of any infectious disease. It is believed to be an important factor in the present severe pandemic of influenza. The virulence of a given strain of microorganism depends upon two variable factors: (1) the toxic properties of the bacteria, and (2) its aggressiveness, or invasive power.

The toxic properties depend on the kind and quantity of toxin or poison which is elaborated. Certain bacteria secrete a toxin during life. It is soluble in the media or surrounding tissue, and therefore is found outside the bacterial body. This is called a true toxin or exotoxin. Such a toxin is produced by the diphtheria bacillus, as well as *Bacillus tetani* and one or two others. The majority of pathogenic bacteria, however, are incapable of secreting an exotoxin. Their toxicity depends upon a poison which is wholly within the bacterial

cell, and which is only liberated when the organism dies and undergoes disintegration. It is in this way that *Bacillus typhosus* and the pneumococcus produce their profound toxemias. Such a poison is termed an endotoxin.

By aggressiveness is meant the ability of a microorganism to invade, multiply, and flourish in the tissues or tissue fluids of the host. This ability must not be confused with toxicity. In most microorganisms the two are intimately associated, but there are one or two excellent examples which readily indicate the fundamental differences involved. Thus the bacillus of diphtheria and the bacillus of tetanus produce powerful toxins, which rapidly bring about most serious conditions in the host, yet these bacteria possess only slight aggressiveness, being seldom found except in the localized areas of infection. On the other hand the bacillus of anthrax is highly aggressive. This is readily shown by the facility with which it penetrates into the blood stream and is carried into all tissues of the body. Sections of tissue from all the organs illustrate how the bacillus flourishes everywhere. Nevertheless it produces little toxin, and infected animals usually show slight signs of toxemia until very shortly before death. Many observers believe death to be due in these instances largely to the mechanical blocking of the capillaries with the anthrax bacilli.

Thus the two terms, toxicity and aggressiveness, must be regarded as separate and distinct, and their combined influence may be summed up in the term virulence, which in turn represents the total disease-producing power of a strain of microorganisms.

While certain bacteria possess an inherently high invasive power, it was shown by Koch that others acquire it under certain conditions. When a tuberculous animal is injected intraperitoneally with a fresh culture of tubercle bacilli, it succumbs quickly to an acute attack of the disease. Bail attempted to explain this on the hypothesis that bacteria may secrete "aggressins" which protect them from the immune bodies of the host, or by directly repelling the leukocytes, prevent phagocytosis. Welch suggested the possibility of such action on the part of invading bacteria when he formulated the hypothesis¹ that bacteria, as living cells, when so placed that they are exposed to the defensive forces of their host, are, under favorable circumstances, stimulated to produce antibodies for their protection. Kolmer² regards aggressins as antibodies of this nature, and considers that they are produced according to the conditions laid down in Welch's hypothesis. Zinsser³ summarizes the basic principles of Bail's theory as follows:

"Pathogenic bacteria differ fundamentally from non-pathogenic bacteria in their power to overcome the protective mechanism of the animal body, and to proliferate within it. They accomplish this by virtue of definite substances given off by them, probably in the nature of a secretion, which acts primarily by protecting them against phagocytosis. These substances (referred to by Kruse⁴ as 'lysins') were named by Bail 'aggressins.' The production of aggressins by pathogenic germs is probably absent in test-tube cultures, or, at any rate, is greatly

depressed under such conditions, but is called forth in the animal body by the influences encountered after inoculation."

Bail's theory has been attacked by different observers, notably Wassermann and Citron,⁵ who claim to have shown that much of the "aggressive" character of Bail's exudates is the result of the presence of bacterial poisons liberated by the disintegration of the microorganism (endotoxins). They claim to have demonstrated a similar action in aqueous extracts of bacteria. Citron⁶ also demonstrated the presence of free bacterial receptors in Bail's exudates, by use of the complement-fixation method of Bordet and Gengou.

Zinsser and Dwyer⁷ have made certain experiments which seem to indicate that Bail's aggressin may be in the nature of an anaphylatoxin. Their anaphylatoxin, when added to an emulsion of bacteria, will convert a sublethal into a lethal dose, and the method of production is similar in principle. Nevertheless it does not explain the immunity produced in animals by Bail's method.

While it is true that aggressin, endotoxin, and anaphylatoxin all increase the effect of a sublethal dose of bacteria, it is likewise true that many indifferent proteins will also exert a similar influence. Thus, Ricketts and Kirk found that a small quantity of egg albumen, broth, or normal serum, when injected into white mice, decrease the resistance of the animals to a concomitant inoculation with tetanus toxin. So, also, it is found by Caulfeild⁸ that the simultaneous injection of the toxin of *Bacillus welchii* with an emulsion of *Bacillus influenzae* into guinea pigs will increase the invasive powers of the influenza bacillus.

Whether the foreign substances preëngage the attention of the leukocytes, so that they have less opportunity to absorb and digest the bacteria accompanying the injection, or whether the foreign substances minimize the direct action of the leukocytes on the bacteria by their general toxic properties, or, lastly, whether these substances merely lower the general defensive mechanism of the animal body by depressing the antibody-producing cells, is not definitely known. Probably all these factors are at work. It is certain, however, that virulent strains of bacteria are not readily phagocyted, while non-virulent strains of bacteria are ingested in large numbers by the same leukocytes. It is possible that this fact bears some relation to the phenomena of so-called positive and negative chemotaxis in the body. Indeed, Adams assumes it to be the same thing.

In connection with the problem of virulence, the work of Walker⁹ is exceedingly interesting. After cultivating the typhoid bacillus upon media containing the serum of an animal immune to this organism, he found that the culture had gained in virulence, and was less readily agglutinated by the immune serum. Moreover, the protective dose of immune serum for an animal inoculated with the organism thus treated was much larger than that required to protect the animal from infection with the untreated typhoid bacillus.

Similarly Danysz¹⁰ showed that by growing anthrax bacilli in a medium containing arsenic, it was possible to increase their tolerance

to this drug as much as fivefold. So, also, Ehrlich was able to develop a strain of trypanosomes which had a remarkable tolerance for atoxyl, Akatsu and Noguchi¹¹ immunized *Treponema pallidum* against large doses of arsphenamin (salvarsan), while Oppenheim¹² likewise found that certain strains of *Treponema pallidum* may acquire a resistance against arsphenamin.

More recently Rosenow¹³ claimed to have demonstrated the presence of protective substances for pneumococci, by growing virulent strains in serum broth. An extract from such a culture would protect avirulent pneumococci from phagocytosis. By leaving avirulent strains in contact with such extracts for 24 hours, it was possible to change them into virulent strains. These extracts were supposed by this author to contain "virulins" which appear to resemble, to some degree at least, the aggressins of Bail.

These observations, therefore, tend to support the view that under certain conditions, microorganisms may develop an immunity on their part toward the defensive mechanism of the animal body, just as the latter is definitely known to produce antibodies antagonistic to the invading bacteria.

A discussion of the question of virulence would be incomplete without reference to the significance of capsules possessed by certain bacteria. Many observers have noted that pneumococci, when freshly isolated from the lungs in cases of pneumonia, are much more virulent than after artificial cultivation. Coincident with this lowered virulence, is the loss of the capsule, which reappears on animal passage, as does the virulence. This, in itself, would not be especially noteworthy, because the pneumococcus is typically a capsulated organism. But when it was found that capsules could often be demonstrated in cultures of bacteria not ordinarily possessing such capsules, if their virulence was raised by animal passage, it was believed that the two properties had a definite relationship. This phenomenon is exhibited by suitable cultures of anthrax bacilli,¹⁴ streptococci,¹⁵ and plague bacilli.¹⁶

Toxins (Bacterial Poisons).—The harmful effects of bacteria are brought about in almost every instance by the poisonous chemical substances produced in some way by their metabolic processes. As we have mentioned in another place, there are possible rare exceptions to this rule, as in capillary emboli in anthrax septicemia, where the death of the animal may be attributed to mechanical harm, but we may assume that save for a few instances, bacteria depend for their destructive properties upon chemical means. These poisonous chemical products are conveniently classified by Wells¹⁷ into four groups:

1. Products of the decomposition of the media upon which the bacteria are growing; among these the best known are the *ptomaines*.
2. Soluble poisons manufactured by the bacteria, and secreted from the cell into the surrounding media—the true *toxins*, or *exotoxins*.
3. Poisons manufactured by the bacteria, which do not escape from the normal bacterial cell, but which are as specific in their poisonous

properties as the true toxins; because of their intracellular situation they are called *endotoxins*.

4. Poisonous protein constituents of the bacterial cell, which form part of the cell protoplasm, but which are not soluble, and the poisonous effects of which are not specific and not usually responsible for disease; these are called *bacterial proteins*.

THE PTOMAINS.*—These are definite chemical compounds of a nitrogenous nature, and may or may not contain oxygen. The simpler forms contain only carbon, hydrogen and nitrogen. Examples of these are:

Methylamin (CH_3)₂NH₂

Dimethylamin (CH_3)₂NH

Trimethylamin (CH_3)₃N

From these formulæ, it is obvious that these simple forms are ammonia substitution products. Ptomains of more complex structure include putrescin ($\text{C}_4\text{H}_{12}\text{N}_2$) and cadaverin ($\text{C}_6\text{H}_{14}\text{N}_2$). Many of the simpler ptomains have little if any toxic effect.

Ptomains were at first thought to be responsible for the toxic effects of bacteria, but were soon found to exist apart from the bacteria themselves, i.e., in the media. In this they resemble the true toxins, but here again a fundamental difference exists in that ptomains are not specific, while toxins are highly specific. Ptomains differ in structure and action, according to the media from which they are derived, whereas toxins produced by a given bacterium always possess the same properties, no matter what the media. It is doubtful if ptomains are ever produced in appreciable quantities in the living tissues. They are commonly found, however, in putrefying meat, especially in imperfectly canned meats, sausages, decomposing fish, cheese, ice-cream and milk.

Although cases of food-poisoning are not uncommon, it is quite seldom that one finds the intoxication due to ptomains. Many of the cases are caused by infections with *Bacillus enteritidis* of Gärtner and with other bacteria related to the colon-typhoid group, such as *Bacillus paratyphosus*. These organisms contaminate the meats and produce an intestinal infection which often is erroneously called ptomain poisoning. Then, too, canned vegetables have been found by Dickson¹⁸ in many instances to contain cultures of *Bacillus botulinus* with its powerful toxin. Indeed, this bacillus was so named because of its occurrence in sausages.

Vaughan, however, isolated a poisonous ptomain from cheese and milk, and it is believed by some that similar substances may be liberated in the intestines as a result of bacterial putrefaction of food incident to faulty digestive conditions. Zinsser suggests that the antagonism to such intestinal putrefaction by the acid production of *Bacillus bulgaricus* is the basic cause of any favorable therapeutic effects observed in Metchnikoff's sour milk theory.

* For a comprehensive consideration of the nature and significance of the ptomains, the reader is referred to Vaughan and Novy, "Cellular Toxins," Lea & Febiger, Philadelphia, 1902.

TRUE TOXINS (Exotoxins).—These are soluble products excreted by the bacterial cells into the culture media surrounding them. They are thus obtained in the broth filtrate of a culture of *Bacillus diphtheriae*, and therefore may be handled quite separately from the organism producing them. They are, so far as is known, uncrystallizable, and in this way differ from the ptomains. They are precipitated along with peptones by alcohol, and also by ammonium sulphate, and in this manner may be obtained in a concentrated form.

Not all bacteria excrete toxins. The best known examples of toxin-producers are the diphtheria, tetanus and botulinus bacilli. The toxins of these microorganisms are highly specific, and have the power of exciting the production of specific antitoxins when injected into animals.

Toxins are relatively unstable, deteriorating rapidly when heated or frozen. The individual characteristics of the more important toxins will be discussed in a later section.

ENDOTOXINS.—These poisons, like the exotoxins, are specific, but are bound firmly to the bacterial bodies during life. Pfeiffer¹⁹ showed that cholera spirilla apart from the broth in which they were grown were strongly toxic. They are only released upon the death and disintegration of the bacteria, whether this occurs within the animal body or *in vitro*. Unlike the true toxins, they do not excite the production of antitoxins when injected into animals.

The great majority of pathogenic bacteria do not form true toxins, but on the other hand, it is probable that they all possess in their living bodies either endotoxin, as we know it, or the requisite substances to form it when the disintegration of the bacterium occurs. This statement infers that it is not yet settled whether this bacterial poison exists as such in the living bacterial cell, or as pro-endotoxin, which upon liberation becomes endotoxin.

BACTERIAL PROTEINS.—Much doubt was cast upon the endotoxin conception of Pfeiffer by the work of Vaughan,²⁰ who showed that proteins can be split by the action of alkali and alcohol into two fractions, one toxic and the other non-toxic. This is true of all proteins, including those of bacterial origin. This observer showed that these toxic split-products are not specific, but possess many of the pharmacological properties of the endotoxins. Thus he was able, by the injection of suitable quantities of toxic split proteins from cultures of *Bacillus subtilis*, to produce rises in temperature which, when charted, bore a striking resemblance to that of typhoid fever. The toxic portion of the protein of typhoid bacilli differed in no essential point from those obtained from many other sources. Friedberger²¹ showed that similar products were found by allowing the bacteria to be acted upon by immune sera in the presence of complement. His results confirmed those of Vaughan both as to the non-specificity of the toxic split-products, and as to the ease of their production from pathogenic and non-pathogenic bacteria alike. Their work led them to the conclusion that the toxic effect produced by the infection was due to the toxic cleavage products liberated by the bacteria during their destruction. Pathogenicity would

therefore depend altogether upon the invading powers, or aggressiveness of the microörganism, and not upon any specific toxic action. They explain the occurrence of characteristic courses of the various infectious diseases, with their differences in type and degree of temperature, symptoms, etc., as due to the location and selective action of the particular microörganism concerned. Vaughan suggests also that specificity of germs may depend upon the non-toxic group in the protein molecule, as it is in these that one protein differs from another. He further states that the body ferments which cause the cleavage of the bacterial proteins in the different infectious diseases are specific.

Method of Action of Bacterial Poisons.—In the case of the bacteria producing true toxins, the damage to the host is accomplished somewhat differently with the different types of microörganisms. Diphtheria toxin is excreted by the bacilli which usually lodge in the mucous membrane of the throat. These bacilli practically always remain localized at the point of infection, but the toxins are absorbed into the circulation, and unite with the various body cells, with resulting damage or death. This is therefore a case of toxemia. With tetanus toxin, on the other hand, the mode of distribution is quite different. Here, again, we have a focal infection at the point of entry of the bacteria, but in this case the toxin, having an affinity for nervous tissue, travels along the nerve sheath toward the central nervous system. Arrived there, it unites with the nerve cells and gives rise to the characteristic symptoms of tetanus. The toxin of *Bacillus botulinus* is unique in that it is able to penetrate the normal mucous membrane of the intestine and thus cause symptoms, after the ingestion of contaminated food. Not even the endotoxin of cholera spirilla is absorbed in this way, and the same is true of *Bacillus typhosus* and of *Bacillus dysenteria*, at least in rabbits,²² and possibly in man. Once in the circulation, however, the botulinus toxin attacks the nerve cells, and the characteristic symptoms and signs develop. The bacillus of botulism does not grow in the body, and for this reason there is *no infection*. All the growth, with the elaboration of the toxin, takes place outside the body, in the contaminated food material, and botulism is therefore, strictly speaking, not an infectious disease, but an instance of poisoning by the ingestion of a biological poison, instead of an alkaloid, as, for example, in the case of strychnin. Certain of the bacterial poisons exert their toxic action upon the tissues of the organs which excrete them. Thus Flexner and Sweet show that although the toxin of dysentery is unable to produce symptoms when introduced into the alimentary canal of rabbits still, once injected into the circulation, it is excreted by the intestinal mucosa and does considerable damage to the cells in the process of elimination. It is considered probable that a similar toxic action is present in the kidneys during excretion, although this is difficult to demonstrate. Typhoid bacilli are excreted through the kidney tissue, and it is possible that the same occurs with tubercle bacilli and with other microörganisms. On their way these bacteria frequently set up foci of infection in the kidney parenchyma. It is probable, therefore, that where the process

does not proceed so far as actual infection, a condition of "subinfection" may exist, in which the endotoxins of the disintegrating bacteria exert their harmful action upon the surrounding tissue cells.

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IMMUNITY

Reference has frequently been made in the preceding pages to the opposition on the part of the host to the infecting organism. Pathogenic bacteria may only invade the tissues when they are able to resist successfully the defensive factors of the animal body. This accounts for the fact that many individuals, known to have been exposed to infecting organisms, do not develop the disease. Thus, it is well known that the dog is resistant to infection by *Bacillus tuberculosis*. This immunity may be natural, as in the example just mentioned; on the other hand, it may be acquired, as in the case of the immunity against small-pox of an individual who has previously suffered from that disease. Inasmuch as he was originally susceptible, the immunity is said to be acquired, and must not be confused with the type in which no such reason for the condition exists.

Natural Immunity.—By natural immunity is meant the resistance to infection which is normally possessed by individuals, races, or species. It is partly due to inheritance; but this statement is only a cloak for our ignorance of the fundamental factors involved. There are, however, certain facts which it would be well to keep in mind, in a

discussion of this interesting and important property of the animal body.

1. **NATURAL IMMUNITY IN SPECIES, RACES, AND INDIVIDUALS.**—(a) It is evident to every observer that certain species are susceptible to a given microorganism, while other species may exhibit a remarkable resistance to the same bacterium. Thus the guinea-pig readily becomes infected by an inoculation of tubercle bacilli, but the dog is relatively immune. The same is true with reference to the anthrax bacilli. It may be, as Zinsser¹ points out, that this variation is due to simple cultural differences such as may exist between carnivorous and herbivorous animals, on account of metabolic conditions. It seems, however, that this simple explanation is not sufficient to account for many of the cases of species resistance, as many microorganisms are pathogenic for both carnivorous and herbivorous animals. In the case of cold-blooded animals, there are varieties of bacteria against which the species resistance seems to be absolute. An example of this is the fact that it is impossible to infect turtles and frogs with anthrax bacilli. Here it is possible that the essential factor is one of simple cultural conditions of which the most outstanding is that of temperature. This view is supported by the experiments of Gibier,² who succeeded in infecting frogs with *Bacillus anthracis* when the frogs were warmed to 35° C.

In the majority of cases, however, species resistance is only relative, and may be broken down in a variety of ways. Thus, if the dose of the inoculation is very large, infection may take place where, under natural conditions, spontaneous infection would never occur. The same result may be obtained by previously or simultaneously lowering the general resistance by chilling or heating, or by actual trauma. A sublethal dose of *Bacillus aerogenes capsulatus* toxin will render a small dose of influenza bacilli capable of producing severe infection in the guinea-pig, if the two are injected at the same time.

The following tabulation by Zinsser³ gives a clear conception of such differences exhibited by various species in relation to the more important organisms pathogenic to man:

“Tuberculosis, human type.—Spontaneously infects man. It is very often observed in monkeys kept in captivity. Cattle, swine and sheep are probably never spontaneously infected; guinea pigs are highly susceptible to experimental inoculation. Cattle, swine, sheep, and rabbits are relatively very resistant to experimental infection. Dogs and goats are still more so. Birds seem to be entirely refractory.

“Tuberculosis, bovine type.—Spontaneous infection occurs in domestic animals, chiefly cattle; it is less frequent in sheep, hogs and horses; it has been reported in dogs and goats. In man infection does occur, but only a small percentage of human tuberculosis is of the bovine type, and these cases are almost exclusively in children. In tabulating 1,042 cases which have been carefully studied, Park and Krumwiede^{*} report the following figures:

* Park and Krumwiede. Jour. Med. Res., 1910, xxiii.

Cases of Tuberculosis in Man (1,042).

Over 16 years—human type 677, bovine type 9.

5 years to 16 years—human type 99, bovine type 33.

Under 5 years—human type 161, bovine type 59.

“The large majority of bovine infections were abdominal, or involved cervical lymph nodes.

“Experimental infection is successful in rabbits and guinea pigs, both of these animals succumbing more rapidly to this than to the human bacillus. In fact, the relative resistance of rabbits to the human bacillus is such that rabbit inoculation is one of the most important methods of differentiating between the two types. Birds are refractory.

“Tuberculosis of the avian type occurs spontaneously in birds. It may be experimentally produced in rabbits (Strauss and Gamaleia). Injected into cattle it causes a local reaction only.

“Tuberculosis of cold-blooded animals is not transferable to warm-blooded animals.

“Syphilis spontaneously occurs in man only. It can be inoculated into chimpanzees, in which primary and secondary lesions develop, corresponding mildly to human syphilis. Primary lesions can be produced in lower monkeys. It can be transferred by intratesticular inoculations to rabbits.

“Gonococcus infection occurs spontaneously in man only. No typical lesions can be produced in experimentally inoculated animals, although death can be caused by large doses, probably by toxic action.

“Influenza bacillus spontaneously infects man only. Experimental infection is partly successful in monkeys only. (Pfeiffer and Beek, *Deutsch. med. Wchnschr.*, 1893.)

“Glanders.—Spontaneous infection occurs in horses and mules; less frequently in sheep, goats and camels. This disease, like plague, may be regarded as primarily a disease of animals, but man may be infected by direct or indirect contact with the diseased animal. All domestic animals may be infected experimentally with ease, except cattle and rats, in which cases large doses are necessary. Birds show local reactions only. (Wladimiroff, in *Kolle und Wassermann Handbuch*, Vol. V, 2nd Ed.)

“Plague occurs spontaneously, chiefly in man and in rats. It has also been found in California ground squirrels, and in hogs, during plague epidemics in Hong Kong. It is highly infectious for guinea pigs and for white rats, slightly less so for mice; rabbits are much less susceptible than guinea pigs. Dogs, cats, and cattle are relatively resistant. Birds appear to be immune. Cold-blooded animals are immune unless artificially warmed. (See above.)

“Malta fever occurs spontaneously in man and in goats. It is pathogenic for all mammals, but it is not fatal for lower animals when the organisms are directly cultivated out of the human body.

“Diphtheria occurs spontaneously in man only. Experimental inoculation is fatal in guinea pigs, rabbits, dogs, cats, and birds. Rats

and mice are highly resistant. The typical pseudomembranous inflammation can be produced in susceptible animals only after previous injury to the mucous membrane, and then it rarely shows any tendency to spread.

"Tetanus is spontaneous in man, horses, cattle, and sheep. It is found rarely in dogs and goats. Birds are highly resistant to experimental inoculation.

"Anthrax is primarily a spontaneous infection of cattle, sheep, and horses; it occurs in man largely through direct or indirect contact with these animals. Guinea pigs, rabbits, and white mice are very susceptible to experimental inoculation. Rats and hogs are less susceptible, and dogs are relatively resistant, although they can be regularly killed by moderate doses intravenously injected. Birds and cold-blooded animals are highly resistant.

"Asiatic cholera develops spontaneously in man only. Rabbits and guinea pigs can be killed by injections of cultures, but die probably of toxemia. In rabbits a cholera-like condition has been produced by injection of the spirilla into the duodenum, after ligation of the common bile duct. (Nikati and Rietsch, *Deutsch. med. Wchnschr.*, Vol. II, 1884, 613.) Ordinarily no multiplication takes place in the animal body. Pigeons are insusceptible, a fact which helps to distinguish this organism from *Spirillum metchnikovi* and other similar bird-pathogenic spirilla.

"Typhoid fever occurs spontaneously in man only. It has recently been produced in a mild form in chimpanzees. Animals are susceptible to the endotoxins, and can therefore be killed by injections of bacilli and extracts, but the organism is not invasive, as in the case of the lower animals. Typhoid septicemia can be produced in rabbits by inoculating them with especially virulent cultures of the bacilli, or cultures previously grown on rabbit-blood agar (Gay). The typhoid-carrier state may ensue for considerable periods in such animals.

"Pneumococcus infection in various forms occurs spontaneously in man. Rabbits, mice, and guinea pigs are highly susceptible. Rats, dogs, cats, cattle, and sheep are relatively resistant.

"Staphylococcus and streptococcus infections may occur in almost all of the warm-blooded animals, chiefly as abscess-producers. In horses a severe form of pleuropneumonia is caused by them.

"Leprosy occurs spontaneously in man only. Lesions simulating human leprosy have been produced in monkeys by inoculation, and partially successful experiments have been made upon the Japanese dancing mouse. Other animals are immune.

"Scarlet fever occurs spontaneously in man only. Monkeys may possibly be susceptible, though not all observers have been successful in such experiments. (Draper and Handford, *Jour. Exper. Med.*, 1913, xvii.) Landsteiner and Levaditi (*Ann. de l'Inst. Pasteur*, 1911, xxv) have succeeded in producing the disease in the chimpanzee, although they failed with lower monkeys.

"Small-pox occurs spontaneously in man only. It is probably identical with cow-pox. (See reasons for this assumption given by Haeussler.)

as cited by Paul in 'Kraus and Levaditi Handbuch,' etc., Vol. I.) It can be experimentally produced in monkeys.

"Measles develops spontaneously only in man. *Macacus rhesus* has been successfully inoculated by Anderson and Goldberger (U. S. Pub. Health Reports, 26, 1911). Other animals are immune.

"Typhus fever occurs in man only. Experimentally it has been produced in chimpanzees, *Macacus*, *Cercopithecus*, *Ateles*, and *Myctes* monkeys. Anderson has succeeded in producing temperature reactions in guinea pigs, by injecting blood from typhus patients, or from other similarly infected guinea pigs. More exact information concerning this disease will probably be available soon, if the reported cultivation of the organism of the disease by Plotz is authenticated.

"Yellow fever up to the present has been observed in man only.

"Poliomyelitis is spontaneous in man only. It can be transmitted to monkeys and, in a doubtful form, to rabbits. No other animals are known to be susceptible."

(b) The racial differences in resistance are also well marked, in many instances. Here, again, the factors at work are much more obscure than may be at first supposed. Cultural conditions are not sufficient to account for the fact that North American Indians are especially prone to contract tuberculosis. The negro also shows the same susceptibility. It is well known that white mice and rats are more easily infected with various organisms than are the gray variety of these animals. Mongolians are said to be immune to scarlet fever, and Carroll⁴ states that white people are more susceptible to yellow fever than are negroes.

(c) Individual differences in resistance to infection may also be quite marked. All laboratory investigators are aware of the failure of certain animals to succumb to inoculations of various organisms, while others of the same species, and indeed, of the same litter, exhibit the greatest susceptibility. So, too, in the human being, it is a matter of common observation that during an epidemic certain members of a family escape unscathed, while others, under precisely the same conditions, have promptly contracted the disease. This has been very noticeable in the present pandemic of influenza. Such individual resistance cannot always be explained by the immunity conferred by a previous attack of the same disease. Nor can it be said that heredity is the main factor involved, although in some cases it has been proved that the offspring may derive from the blood of the mother, before birth, immune bodies which for a time confer a passive immunity. This is well illustrated in diphtheria; but in these instances the immunity is the result of antibodies circulating in the blood. This is not usually the case in natural immunity, for it is found that natural immunity cannot be transferred passively from one individual to another, as in acquired immunity, and therefore, cannot depend upon antibodies circulating in the blood, but rather upon certain cellular characteristics inherent in the individual. In this connection, it seems more than likely that the general condition of the individual may have a very important

bearing upon the question. It is reasonable that the weakly member of a family should not be able to throw off an infection which can gain no headway in the more sturdy members. It may be, therefore, that it is another instance of the law of the survival of the fittest.

However, these considerations only serve to elucidate the more obvious phases of the question, since the fact remains that the true fundamental factors involved in many of the phenomena of natural resistance still remain a closed book. Until we are able to demonstrate the action of the cellular influences, other than those concerned in the production of the antibodies at present known, we shall be forced to accept the fact of natural immunity without an adequate explanation.

2. FACTORS CONCERNED IN NATURAL IMMUNITY.—There are, however, certain factors entering into the production of a spontaneous, or natural resistance, which are more or less well understood. These factors may be summarized under the following captions:

- (a) Surfaces and secretions.
- (b) Phagocytosis.
- (c) Natural antitoxic immunity.
- (d) Natural antibacterial immunity.
- (e) Atreptic immunity.

(a) *Body Surfaces and Secretions.*—The skin is, in most cases, a very effectual natural barrier to the infecting organism. It has been found that very few bacteria have the power to penetrate the unbroken skin. Staphylococci may be rubbed into the skin and succeed in producing infection, for the reason that the rubbing damages the epithelium and forces the organism into the hair follicles and sweat glands, where it is able to proliferate and invade the tissues. There is some evidence to support the view that the *Spirocheta pallida* may enter the unbroken skin, but this is difficult to prove, inasmuch as the organisms producing chancres upon the skin may have found a microscopic abrasion or defect, through which they entered to the subcutaneous tissues. Where abrasions or wounds do occur, the serous exudate, and the scab or crust which subsequently forms, are antagonistic to infection. This action of the serum is due to its antibacterial qualities, of which we shall speak later. The scab merely forms a mechanical barrier.

The subcutaneous connective tissue forms the next line of defense, should the skin prove defective. Here the mechanical barrier is not absolute, but tends to restrict the invasion of the microorganisms to the superficial tissues. The anti-bacterial action of the serum in the subcutaneous tissues is also important. Tuberculosis of the skin is, for these reasons, much more easily controlled than when it attacks the viscera. The same is to some extent true of anthrax in man.

The mucous membranes are a very efficient protection from bacteria, although they are usually called upon to deal with much larger numbers than is the skin. This is due to the warm, moist surface which favors the growth of bacteria. The viscid mucus forms a barrier, and

at the same time tends to carry away microorganisms. Diphtheria bacilli, however, always produce infection by way of the mucous membrane, except perhaps in open wounds, as Fitzgerald and Robertson⁵ pointed out in connection with wounded Canadian soldiers. Gonococci likewise require mucous membrane, particularly simple columnar epithelium, through which to gain entrance. Later they may attack serous surfaces as synovial membrane and endocardium.

In the nasal cavity, the moist projections of the turbinates intercept most bacteria entering by the anterior nares, and thus the mucous membrane is constantly covered with microorganisms. The ciliated epithelium tends to eject these with the secretions, but chronic infection is very common and may extend to the accessory sinuses, where drainage is poor, and toxic absorption is more favored.

Enormous quantities of bacteria flourish in the mouth, commonest among which are *Streptococcus viridans*, pneumococci, staphylococci, *Micrococcus catarrhalis*, and diphtheroid bacilli. The saliva is not bactericidal, but is said to inhibit the growth and lower the virulence. The streptococci found in this locality is of very low virulence, requiring tremendous doses to successfully infect mice or rabbits. Nevertheless, these strains have been shown by Detweiler and Maitland⁶ to be capable, under suitable conditions, of producing malignant endocarditis and many other lesions in rabbits.

The tortuous channels through which the air passes on its way to the lungs act as filters for the bacteria. It is probable that the inspired microorganisms seldom, if ever, reach farther than the bronchi before adhering to the mucous membrane. At this point they may set up an infection and either by continuity of tissue, or by lymphatics or blood stream, reach the alveoli. The cilia of the epithelium, the mucous secretion and the mechanical effect of coughing, all tend to expel the bacteria before they penetrate the mucous membrane.

The stomach receives many bacteria with the food, which is always contaminated before being taken, and which gathers many more bacteria while being masticated in the mouth. The hydrochloric acid of the gastric juice, however, effectually disposes of the great majority, so that the contents of the duodenum are comparatively free from organisms. Nevertheless, it is apparently inadequate in many instances, for such invaders as typhoid bacilli, cholera vibrio, dysentery bacilli, and *Bacillus tuberculosis* may pass through to the intestine, where they penetrate the epithelium and invade the tissues, producing their characteristic lesions. The bile is weakly antiseptic, although it dissolves pneumococci; typhoid bacilli, on the other hand, thrive in a bile medium.

Within a few hours after birth, the intestine shows the presence of numerous bacteria, some of which, as the colon bacilli and streptococci, are pathogenic, though of low virulence. The mucous membrane becomes accustomed to these microorganisms, which live a saprophytic existence, and seldom does it become infected or show signs of injury as a result of their presence. Even the bacillus of Welch is often a normal in-

habitant of this tract without obtaining entrance into the tissues. On the other hand, the bacteria ordinarily causing intestinal infection (typhoid, dysentery, tubercle, and cholera) are not normal inhabitants.

The genito-urinary surfaces do not present any protective features, other than those described above. The acidity of the vagina may be mentioned as an inhibiting influence, although the bacillus of Döderlein is normally present in this area. The urinary irrigation is believed to be important in the cleansing of the urethral mucous membrane, which beyond the meatus is sterile in normal individuals.

(b) *Phagocytosis*.—The cellular theory of immunity was particularly elaborated and championed by Metchnikoff and his pupils. In studying the activities of the amebæ under the microscope, Metchnikoff noted that when they came into the vicinity of particles of matter suitable as food, they sent forth elongations of protoplasm (pseudopodia) toward the food particles. In this way the latter were finally engulfed and appeared within the cytoplasm of the amebæ. After a time the particles became fainter and fainter, and finally disappeared—in other words, they were digested. Similarly he noted minute ameboid cells within the body of the daphnia, a small crustacean, which had the power to ingest and digest, in the same way, yeast cells which had gained entrance into the body of the daphnia. He also noted that if the yeast cells were too numerous, the wandering cells could not cope with them, and the daphnia would succumb. It was quite apparent, therefore, that the wandering cells played an important part in protecting the crustacean from destruction by the yeast cells.

Furthermore, Metchnikoff noted that anthrax bacilli, injected into the frog, were ingested and destroyed by the wandering cells (leukocytes), which he felt were responsible for the immunity of the animal to this infection. The same phenomena were observed in many infections, both in the lower animals and in the human body. This ingestion of the microorganisms, and their subsequent digestion, Metchnikoff termed phagocytosis, the wandering cells which accomplish it being called phagocytes. Typical film preparations of pus from cases of gonorrheal urethritis, and of meningococcal meningitis illustrate phagocytosis in a marked degree.

Subsequent investigations have amply shown that not only natural immunity, but even to a greater degree, active immunity is accompanied by an increase in the phagocytic process. At this time, the work of Wright and Douglas⁷ set forth the important part played by the blood-serum in the process of phagocytosis. They showed that leukocytes which were washed free of all traces of serum did not ingest bacteria, or, at least, did so only slightly. If, however, normal serum was added, phagocytosis became more marked, and if serum from an animal highly immunized against the bacteria in question was used, the leukocytes exhibited the most marked activity. The substance in the serum which brought about this activity was named by Wright "opsonin." Its action was shown to be upon the bacteria, and not upon the leukocyte, as the latter can be washed free of opsonin-containing serum,

but bacteria, once exposed to opsonins, cannot be washed free of them. The nature of opsonins will be discussed in a later section.

Metchnikoff classified phagocytes into two groups:

1. **Macrocytes or Macrophages.**—These are large mononuclear cells, and certain fixed tissue cells, particularly of the spleen, liver, lungs and lymph-nodes. They are active in the removal of necrotic tissue, injured blood-cells, and in chronic bacterial infections, notably in tuberculosis, leprosy and actinomycosis. They contain a digestive enzyme, "macrocytase," which digests these materials or cells.

2. **Microcytes or Microphages.**—These are polymorphonuclear leukocytes. They engulf bacteria and similar cells. They contain "microcytase," which dissolves or digests bacteria.

Metchnikoff believed that the digestion of the bacteria within the phagocyte was accomplished by an enzyme which is produced by the leukocyte, and is not found free in the blood-plasma. This enzyme he believed to be identical with Bordet's alexin (Ehrlich's complement). Much experimental work has been done to establish whether this is really found only in the leukocyte or whether it normally exists free in the plasma or serum. Gengou collected the blood of various animals into paraffined tubes, so as to injure the cells as little as possible. He claimed that in the plasma of such blood he could detect little or no alexin, whereas in the serum obtained in the ordinary way the usual amount was present.

This observation has not been confirmed, but the majority of workers at the present time believe that the complement or alexin is normally present in the circulating plasma. Zinsser points out, however, that a really crucial experiment to prove this has not yet been formulated.

It is likely that the lysis of bacterial and other cells in the serum or plasma is accomplished by ferments which are quite distinct from those within the leukocyte. As Zinsser suggests, it is probable that the digestion of ingested bacteria is brought about by a complicated process involving not one, but several ferments.

Where the infection is a localized one, as in a furuncle or boil, we have a good example of the phenomenon of phagocytosis. In a very short time after its inception the infection has attracted large numbers of polynuclear leukocytes and these are beginning to ingest numbers of the bacteria present. If the virulence of the invading organism is very high, few, if any, leukocytes are found either in the neighborhood of the lesion, or in the circulating blood. In the first instance we have an example of what is called, for want of a better term, "positive chemiotaxis." In the latter it is a case of "negative chemiotaxis." Exactly what is involved in these terms is not fully understood. From the work of Leber⁸ and Buchner,⁹ it is obvious that bacterial cells are able to produce, either during life or after their death, substances chemical in nature which are able to attract leukocytes.¹⁰ But the observations of Massart and Bordet¹⁰ show that it is not bacterial proteins alone but also products of disintegrated tissue cells and leukocytes which

possess this property. This would appear to explain the attraction of leukocytes to injured areas, and to areas of inflammation of non-bacterial origin.

As for negative chemiotaxis, it may be that bacteria develop an immunity to the defenses of the host, as suggested by Welch, and that they may give rise to aggressins (Bail), virulins (Rosenow), or free receptors which, circulating in the blood, exert a depressant action upon the leukocytes. We cannot at the present time definitely solve this problem. It is difficult to explain why in certain diseases, such as lobar pneumonia, there is usually a marked leukocytosis, while in others, as typhoid fever or influenza, a leukopenia is almost invariably the rule. The virulence of the microorganism concerned is not the only factor, although a low leukocyte count in lobar pneumonia is considered a matter of grave import. Similarly, in cases of acute infections in the abdomen, the surgeon is reassured on finding a marked leukocytosis present, believing that to be an indication of a vigorous reaction against the bacteria on the part of his patient.

While it is true that phagocytosis is less marked as the virulence of the microorganism is raised, it is also true that sometimes if the virulence is very low the phagocytosis is quite sluggish. Thus in chronic gonorrheal infections the bacteria which, when the infection was fresh, were almost invariably phagocyted, are often extracellular. It is possible that here the opsonic content of the blood is low, since the antigen (gonococcus) has lost much of its original potency by a lowering of its virulence, as the infection becomes chronic. This would explain the lessened phagocytosis. It would also explain the absence of phagocytosis where the organisms are excessively virulent, as in this case the antigen is too powerful to allow of the optimum reaction on the part of the body cells, as evidenced by the opsonic power.

(c) *Natural Antitoxic Immunity*.—There is evidence to show that natural immunity to certain diseases may depend, in part, if not altogether, upon the natural antitoxic content of the blood. Otto¹¹ showed that more than 1/100 of a unit of diphtheria antitoxin is present in each c.c. of the blood of persons who had been in close contact with cases of diphtheria without having been ill themselves; others usually had much less. He also found that diphtheria carriers, both those who had had the disease and those who had not, contained more antitoxin in their blood than did patients who had just recovered from an attack. Recently Schick published a method of estimating the antitoxin content of blood. A minute quantity of toxin is injected intracutaneously, and a local reaction follows if there is less than 1/30 of a unit of antitoxin per c.c. of blood. This amount is considered sufficient to protect against diphtheria. Many observations tend to show that even 1/100 of a unit per c.c. is ample. The Schick reaction has been used to test a large number of normal individuals of all ages. Negative reactions have been obtained in 93 per cent. of the newborn, in 57 per cent. during the first year of life, in 37 per cent. between two and five years, and

in 50 per cent. between five and fifteen years. In adults the negative reactions are as high as 90 per cent.*

(d) *Natural Antibacterial Immunity*.—In 1881 Lord Lister reported observations upon the resistance of the blood to putrefaction. This was first noted by Hunter, and later by Traube, but in 1884 Grohman¹² definitely stated that blood-plasma possessed the property of inhibiting the growth of bacteria. In 1888 Nuttall¹³ showed that the cell-free defibrinated blood of normal animals actually destroyed microorganisms, and Buchner¹⁴ demonstrated that this bactericidal property resided in the serum. The serum of the dog and of the rat possesses bacteriolysins and bacteriotropins (opsonins) against anthrax bacilli.

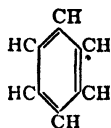
(e) *Atreptic Immunity*.—Ehrlich found that upon transferring mouse cancer to rats, the tumor soon died. He assumed that this outcome was due to the lack of suitable nutritive material in the rat for that type of tumor. To this condition he gave the name "atrepsia." In the same way it is held that one factor in natural immunity to bacterial infection may be the lack of suitable food in the host for the microorganism. This is somewhat similar to the "exhaustion theory of immunity" advanced by Pasteur, but as Ricketts and Dick¹⁵ point out, there is a difference, in that Ehrlich did not assume the *absence* of suitable nutritive material, but the *inability* of the bacteria to secure it. As they put it, "virulent microorganisms find the nutritive substances already available, or, if this is not the condition, the injury which they effect upon the tissues in the first instance results in a splitting of the constituents so that the food substance (rather a specific food substance) becomes available. Avirulent organisms not having the power to produce this splitting result, do not proliferate to any great degree, and soon become the prey of the protective agencies such as the leukocytes and bacteriolysins."

While there is no definite experimental proof of this atreptic theory of immunity, it does not seem improbable that it may be one of the factors concerned in the general condition which renders the animal body naturally immune to a given microörganism.

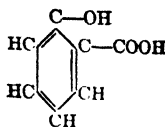
3. *EHRLICH'S SIDE-CHAIN THEORY*.—The humoral theory of immunity received its greatest prominence through the work of Ehrlich. In 1885, five years before the discovery of antitoxin by von Behring and Kitasato, Ehrlich elaborated a theory to explain the process of nutrition of the body cell. He held that the assimilation of food by cells is accomplished only after a chemical union has taken place between the food substance and some constituent of cell-protoplasm. He spoke of that portion of the cell which carries on the central activities as the "*Leistungskern*," or vital portion of the cell, while those constituents which came directly into contact with the food substances were called side-chains of the cell. Analogous to this conception in chemistry is the central benzol ring, to which are attached side-chains to form various other compounds. Thus, just as the side-chains of the cell may unite with food substances, so the side-chain of the benzol ring may unite with

* These figures are quoted from Park and Williams, "Pathogenic Bacteria," 1917.

groups of atoms to form slightly varied compounds. Thus, salicylic acid is formed by the attachment to one of the side-chains, of a hydroxyl group and to another of the acid radical.



Benzol Ring



Salicylic Acid

Ehrlich held that a cell possesses two important functions. The first is a special physiologic function, such as contractility in muscle cells, conductivity in nerve cells, secretion in gland cells, etc. The other is that of nutrition, and it is this function which has to do with the problem of immunity.

After the discovery of von Behring that in certain diseases the blood possesses definite protective substances against bacterial toxin, Pfeiffer discovered the presence of bacteriolytic substances in peritoneal exudates of guinea pigs previously inoculated with cholera vibrios. Bordet showed that this phenomenon was due to two distinct substances. One is the amboceptor, or "substance sensibilitrice," which is specific, and therefore exists only in the animal which has been immunized against that particular bacterium; the other he called "alexin," which is non-specific, and exists in the blood of practically all animals. These discoveries gave fresh support to the humoral theory of immunity, and Ehrlich's side-

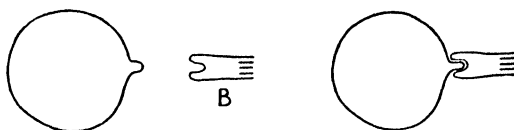


FIG. 1.—EHRlich's SIDE-CHAIN THEORY, SIDE-CHAIN OF THE FIRST ORDER.

- A, Body-cell with side-chain of the first order.
 B, Toxin molecule (antigen).
 C, Antigen attached to side-chain of cell.

chain theory of nutrition was adapted to explain the questions arising as new observations were made.

Ehrlich assumes that a toxin molecule is composed of two essential parts: One is the "haptophore" group, and its function is to unite the toxin to the receptor or side-chain of the cell. The other is the "toxophore" group, and is responsible for the toxic action of the molecule.

Evidence of such dual constitution on the part of the toxin molecules is not lacking. Morgenroth¹⁶ has shown that tetanus toxin injected

into frogs will disappear (slowly); but if the animals are kept at a low temperature they show no toxic symptoms. The disappearance of the toxin from the circulation indicates that it is bound by the cells, as indeed can be shown *in vitro*, but at the low temperature the toxophore molecule does not functionate. If the animals are warmed to 30° C. or more, they gradually show signs of tetanus and succumb to the disease. This illustrates in a striking way the presence of haptophore and toxophore groups in the toxin molecules.

According to Ehrlich's theory, a toxin molecule or "antigen" of any kind, upon approaching a body cell, selects a suitable side-chain or receptor with which to unite. The cell is supposed to possess an innumerable variety of receptors designed to "fit" the various toxins and other substances which occur in the blood stream. Only a certain number of receptors of each cell are suitable for a given toxin molecule. The union of these two elements is selective; to use the words of Fischer, they must fit each other "like a key fits a lock."

After this union takes place, the particular side-chains affected can no longer take part in their function of uniting with food substances. They are therefore rendered useless to the cell to which they belong. More than that, the toxophore group of the toxin molecule may now exert its injurious action, and damage the cell. If a sufficient number of toxin molecules are present to unite with the suitable receptors of the cell, sufficient injury may be done to cause the death of the cell, and if a large enough number of cells are thus destroyed, symptoms of disease follow, and the process may go on and cause the death of the animal. If, however, the toxin present is only sufficient to partially disable the cells, the latter may react in a very striking manner. So long as the receptors, to which the toxin is bound, are attached to the cell, the physiologic functions are interfered with. These may be cast off free into the blood stream, as neutralized toxin. In the meantime the cell is busy repairing the damage done. It develops new receptors of the kind it has lost, and according to the overproduction theory of Weigert, if sufficient stimulus to repair is provided (in the presence of additional supplies of toxin from time to time), the cells will continue to make receptors even after those lost have been completely replaced. These extra receptors find no room for attachment to the cell which produced them, and are cast off free into the circulation. They retain, however, the same combining power as the receptors which are still attached, and thus are just as efficient in the neutralization of toxin. These circulating receptors constitute what are known as immune bodies, or antibodies, and in the case where the antigen is a toxin, the free receptors are called antitoxins. The side-chains, or receptors, which unite with toxins or simple ferments, are termed side-chains of the first order. Those more complex, which unite with the precipitable and agglutinable substances of bacteria, are called side-chains of the second order. There are others still more complex, which are bound by lytic substances of bacterial or animal cells. These are receptors of the third order.

(a) *Side-chains of the First Order* (Antitoxins, Antiferments).—The simplest receptor or side-chain of the cell is composed of a single arm (see Fig. 1). This serves to bind the haptophore groups of a molecule of food, or a molecule of toxin. When the latter is circulating in the blood, it comes into contact with the receptor, and is bound to the cell by that agency. As previously explained, the toxin molecule is composed of a haptophore group which unites the molecule with the receptor, and a toxophore group which thereupon proceeds to exert a toxic action upon the cell. If this toxic action is not excessive, the only damage done is to put out of function a number of receptors which the cell requires for the anchoring of food particles. An attempt is then made to regenerate these necessary side-chains. The effort does not stop, however, at merely replacing those lost, but, after the manner pointed out by Weigert, the cell produces a number greatly in excess of the actual needs. Adam points out that the antigen—in this case the toxin—enters into intimate relationship with the cell, through the haptophore group, and the prolonged stimulation of its presence is responsible for the excessive production of receptors. This factor supplements the over-production tendencies in tissue repair. These receptors cannot all be accommodated upon the surface of the cell, and are consequently cast off into the circulation. They are now called antitoxins by virtue of their ability to unite with the haptophore group of toxin molecules and, having done so, the toxophore group is rendered innocuous, inasmuch as there is no cell to act upon. This really amounts to a neutralization of the toxin. The receptors produced as a result of the stimulation of the cell by the presence of toxin are specific. Thus tetanus toxin induces the production of receptors (antitoxins) which neutralize tetanus toxin only. This is true of those antibodies induced by any substances capable of stimulating the body cells in this way. These substances which call forth the production of antibodies or receptors are termed “antigens” and each type of receptor or immune body (antibody) is specific for the antigen which stimulated its production.

In the production of antibodies, the haptophore group is probably the essential part of the antigen. This is true at any rate of the toxin-antitoxin reaction. Where the toxophore group of the toxin molecule is lost, but the haptophore group remains intact, as occurs in the deterioration of toxin on standing, the resulting substance is called by Ehrlich “toxoid.” This really represents unenumerated haptophores. Now, it is found that inoculations with toxoid will result in the production of true antitoxins in no way different from those produced when toxin is used as the antigen. It is seen from this that the toxophore group in itself possesses little or no antigenic value, although it is found that when it is present the production of antitoxin is much more vigorous. This is probably due, as pointed out by Kolmer, to the stimulating effect of the intact toxophore group of the toxin molecule.

(b) *Side-chains of the Second Order* (Agglutinins and Precipitins).—Going back again to the nutritional phase of cell function, we find that Ehrlich assumed that if substances of greater complexity are needed

as food for the cell, some preliminary treatment in the way of digestion is required to prepare these substances for assimilation after they are bound to the cell. A side-chain of the first order possesses merely a binding group, and has no provision for digestion of the food particle. Consequently these more complex food substances are taken care of by side-chains possessing, in addition to the haptophore or combining group, a zymophore or digesting group. These are called side-chains of the second order. Side-chains, similar to or identical with these, are present to deal with bacterial cells. Produced in abundance owing to the presence of the antigen (bacterial cells) in the body of the host, these side-chains of the second order are thrown off free into the circulation, just as are those of the first order. Their action, however, is different. Upon combining with the antigen, which, let us say, is composed of typhoid bacilli, they cause the bacteria to clump together, or "agglutinate." If the bacteria are first dissolved or extracted, and

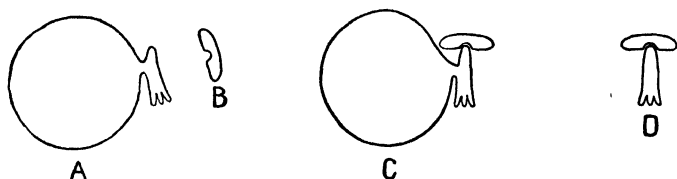


FIG. 2.—EHRlich's SIDE-CHAIN THEORY, SIDE-CHAIN OF THE SECOND ORDER.

A, Body-cell with side-chain of the second order.

B, Bacterial antigen.

C, Antigen attached to side-chain of body-cell.

D, Side-chain cast off from cell, and attached to bacterial antigen.

the resulting clear fluid containing their soluble proteins is brought into contact with the serum containing the side-chains, a precipitate is formed. The side-chains, or immune bodies, which cause agglutination of the bacteria, are called *agglutinins*, and those which cause precipitation with protein solution are called *precipitins*.

The haptophore group of these side-chains is relatively stable, but the zymophore group is labile and may become inactive without a corresponding deterioration of the haptophore or combining group. A powerful agglutinating serum, if heated to 60° C., or kept for a long time, will lose its power to clump or agglutinate. It does not, however, lose its combining power, as is shown when it is allowed to stand in contact with its antigen (emulsion of bacteria). Upon washing the antigen thoroughly and then placing it in contact with *fresh*, powerful agglutinating serum, clumping fails to take place. This is due to the fact that the antigen has been bound by the side-chains, which have lost their zymophore groups. Such side-chains are called *agglutinoids*.

Similar deterioration occurs in the case of precipitins. These changes in immune bodies or antibodies closely resemble the changes occurring in a toxin (antigen) producing toxoids.

The rôle played by side-chains of the second order (agglutinins and precipitins) in immunity is not yet understood. It has not been shown that they actually destroy the bacteria or other protein with which they combine. Agglutinated typhoid bacilli may still be successfully cultivated upon artificial media, showing that they have not been killed, though their motility has disappeared. Again, immunity may exist in an inoculated animal after the agglutinins have disappeared completely from the blood.

(c) *Side-chains of the Third Order* (Cytolysins, Hemolysins, Bacteriolysins, Cytotoxins).—Food substances of still greater complexity are dealt with by the aid of more elaborate side-chains or receptors, according to Ehrlich. These receptors possess a haptophore group by which they anchor the food molecule, and a second haptophore group by which they unite with a special ferment-like substance in the blood called alexin (Buchner) or complement (Ehrlich). In this way, these receptors act as connecting links between food molecule and complement, and the food is digested by this combination. Similar receptors are supposed to be present in an immunity to complex antigens, such as bacterial cells, blood-cells, and cells of various organs. Such receptors were called by Ehrlich amboceptors (substance sensibitricæ, Bordet). The lysins, i.e., hemolysins, bacteriolysin, and other cytolysins, are antibodies of this type. They are specific, as are the antibodies of the first and second orders.

In accomplishing their lytic action, these amboceptors or antibodies first unite with the antigen. The latter is then said to be "sensitized," but no lytic action is apparent until a complement is anchored to this combination. The following experiment will serve to illustrate these facts:

1.

antigen	+	amboceptor	+	complement	hemolysis
(sheep red cells)		(anti-sheep hemolysin)			

antigen	+	complement	=	no hemolysis
(sheep red cells)				

Let stand for 1 hour at 37° C.
Then wash in saline. Now add
amboceptor; no change.

3.

antigen	+	amboceptor	=	no hemolysis
(sheep red cells)		(anti-sheep hemolysin)		

Let stand for 1 hour at 37° C.
Then wash thoroughly in saline.
Now add the complement, and
hemolysis will occur.

This illustrates graphically the close union of antigen with amboceptor (sensitization), a union not disturbed by repeated washing in saline solution. Nevertheless, no lytic action takes place until the complement is united to the sensitized antigen.

Side-chains of the third order may, therefore, be graphically illustrated as receptors possessing two haptophore groups.

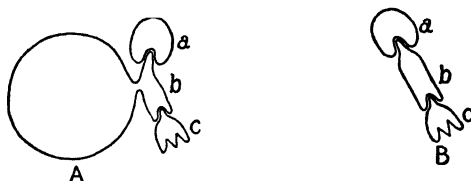


FIG. 3.—EHRlich's SIDE-CHAIN THEORY, SIDE-CHAIN OF THIRD ORDER.

A, Body-cell with side-chain (b), uniting antigen (a) and complement (c).

B, Side-chain (b), free in circulation, attached to antigen and complement.

These side-chains, or amboceptors, play an important part in the phenomena associated with "complement-fixation," which will be discussed in its proper place.

Acquired Immunity.—Having taken up the outstanding features of a natural resistance to infection, it becomes our duty, now, to study the type of immunity which is acquired by the individual as the result of the reaction to certain factors, either known or unknown. It has long been known that a person who has recovered from an attack of small-pox seldom if ever suffers from a subsequent infection of the same nature. Similarly, in typhoid fever, a second attack is very rare. If we inquire into the processes by which such immunity is gained, we find that almost universally it involves more than one type of antibody. It is probable that many factors take part in the production of such a condition, and we know that these factors vary considerably in the case of different diseases. Thus in either natural or acquired immunity to anthrax, phagocytosis seems to be the main factor in the resistance shown. In immunity to cholera spirillum, on the other hand, the protection seems to be due mainly to lytic substances in the blood and tissue fluids. This is well shown by the classical "Pfeiffer phenomenon" described in the chapter on bactericidal substances. In this way, we may speak of certain cases of immunity as antibacterial, of others as antitoxic, and of still others as phagocytic.

Acquired immunity may be defined as *the resistance of the body to a disease by reason of protective substances having been developed in the body as the result of (1) a previous attack of the disease in question, or (2) artificial inoculation with the causative microorganism, either in its original state or in some modified form, or (3) artificial inoculation with the antibodies corresponding to the causative microorganism.*

Acquired immunity may be either *active* or *passive*. In active immunity, the cells of the individual possessing it have produced, or are

producing, the protective substances responsible for the resistance to disease. In passive immunity the protective substances are supplied to the body "ready-made."

METHODS OF PRODUCING ACTIVE IMMUNITY.—In general, it may be said that all methods designed to produce an active immunity are based upon the fundamental principle that the antigen must be introduced into the animal body in suitable amounts, and at proper intervals, in order that the body-cells shall not be overwhelmed by the toxic products of the antigen on the one hand, and shall be sufficiently stimulated to react, on the other.

In the early work on active immunization, numerous methods were tried with more or less success. One of the earliest was that of *inoculation with living but attenuated cultures*. Pasteur was one of the first to employ this method in his work on the immunization of sheep against anthrax infection. Here he reduced the virulence of the organism by growing it at high temperatures. He accomplished the same purpose in connection with rabies immunization by drying the spinal cords of rabbits infected with rabies virus. The method is still largely in use for prophylaxis against this disease. The Jennerian vaccination against small pox is an example of the same principle, but here the attenuation is produced by passing the virus through calves, although the original vaccine was obtained not by experimental procedures, but by the natural passage through cattle. Toussait attenuated his anthrax antigen by heating it to 55° C. for 10 minutes, while Chamberland and Roux¹⁷ accomplished the same purpose by growing anthrax bacilli in the presence of antiseptics, such as carbolic acid 1 to 600.

Another method which has been employed by various workers from time to time is that of *inoculation with virulent cultures in minute amounts*. It is reasonable that living virulent cultures would resemble much more fully the antigen, as represented by the microorganisms actually producing the disease. It is more than probable that the heating or other methods of attenuation of the culture has the effect of in some way lessening or altering the antigenic properties of the bacteria.

It is possible to immunize animals against even such virulent organisms as *Bacillus anthracis*, by using exceedingly small doses of the fully virulent culture. Thus Webb, Williams, and Barber,¹⁸ by a special technic, were able to begin the immunization of animals by the injection of a single thread of anthrax bacilli. They then gradually increased the amount until comparatively large doses were tolerated.

In general, however, it would seem wise to restrict the use of such methods to laboratory animals rather than to risk the danger of fatal infection in the human body. Living vaccines of less virulent types of microorganisms such as *Bacillus typhosus*, cholera spirilla, and plague, have been successful in the hands of Gay,¹⁹ Strong,²⁰ and Metchnikoff and Besredka.²¹ The latter, as well as Gay, report the advantage of using what is called "sensitized" vaccines. These are emulsions of microorganisms which have been subjected to the presence of their specific immune serum, during which time the bacteria unite with the

immune bodies or are "sensitized." This union is quite firm, and lasts until the bacteria inoculated into the patient find themselves in the presence of a complement, when the usual serum reactions, bacteriolysis and possibly phagocytosis, occur. It is claimed for such vaccines that the antigenic substances are thus more quickly taken up by the tissue cells, and that a more rapidly ensuing immunity develops. Furthermore, it is claimed that with sensitized antigens there is much less local and general reaction on the part of the patient, and that larger doses are in this way easily tolerated.

In using living vaccines, however, there is always the danger of their becoming too virulent and thus producing disease, or of producing chronic "carriers" who would be a source of infection to others. These disadvantages probably outweigh the apparent advantages, and preclude their use in human practice.

The method most extensively practiced in the immunization both of human beings and of laboratory animals, is that of *inoculation with dead bacteria and bacterial extracts*. It was probably first employed clinically by Koch in his tuberculin treatment, and later was popularized and extensively used by Wright and his associates. Wright worked almost wholly with saline suspensions of killed organisms. As stated before, it is quite probable that the immunity thus produced is not as complete or efficient as that following recovery from infection, or that following inoculation with a suspension of the living bacteria. It is, however, much safer.

The microorganisms are killed usually by heat, and this seems to be an important factor. It has been found that the antigen value of a vaccine is greater if the temperature is kept as low as possible while killing the bacteria. Most laboratories employ a water bath at from 55° C. to 56° C. When such low temperatures are used, one must be careful to control the sterility of the product by proper cultural tests. The common method of preparation is as follows: A culture of the microorganism is grown on an agar slant for 24 hours. Five c.c. of sterile physiological saline solution are added, and the culture lightly scraped off the slant into the saline solution. If a larger amount is needed, additional or larger slants are employed. The emulsion thus obtained is collected into a sterile tube which is sealed off in the flame and shaken vigorously by hand, or in a mechanical shaker, until the bacterial clumps are completely broken up. The time necessary for this procedure varies greatly with the type of bacteria being dealt with. Suspensions of *Bacillus typhosus* and staphylococci are easily dealt with, but certain strains of streptococci and *Bacillus pertussis* must be agitated for several hours. Sterile glass beads are often used to aid in the process.

The suspension is now ready to be standardized. This is best accomplished by counting the bacteria contained in a unit volume of the suspension by one of the methods outlined below. A small amount may be withdrawn from the tube for this purpose:

(a) *Wright's Method*.—With a capillary pipet draw two per cent.

sodium citrate solution to a mark about an inch from the tip, then allow a bubble of air to enter. Next draw one volume of blood from a finger-prick, another bubble of air, and lastly one volume of bacterial suspension. Now expel the whole onto a clean glass slide and mix thoroughly by sucking up and expelling several times. Finally make two or three films on glass slides in the same manner as one would make a blood film for differential examination. These are dried in the air, fixed by immersing for two minutes in a saturated solution of bichlorid of mercury, washed thoroughly and stained with carbol-fuchsin 1-10 for one minute. Wash and allow to dry.

For accurate counting the microscope field should be reduced in size by placing a paper diaphragm with a small square opening on the diaphragm of the eye-piece. Corpuseles and bacteria are counted in many fields selected at random. The total number of blood-cells are now compared with the total bacteria. Since equal volumes of blood and suspension were taken, and since there are 5,500,000 corpuseles in one cubic millimeter of blood, the formula would be:

$$\frac{5,500,000}{\text{No. of corp.}} \times \text{No. of bacteria} = \text{No. of organisms per c. mm. of suspension}$$

(b) *Thomas' Method.*—The bacterial suspension is drawn up in an ordinary red blood-cell counting pipet to the mark 0.5 followed by freshly filtered carbol-thionin, Leishman's or Jenner's stain, sufficient to stain the bacteria. After mild agitation for two to three minutes, the bulb is filled to the 101 mark, and after thorough dissemination of the bacteria, a drop of the pipet content is placed on a hemocytometer chamber, and the microorganisms are counted, just as are red blood-cells. The cover-slip should not be more than 0.13 mm. thick, in order not to interfere with the oil-immersion lens.

Having estimated the number of bacteria per c.c. of the suspension, it is diluted with sterile saline solution to the desired strength. 0.5 per cent. pure phenol is added, and the resulting mixture cultured for sterility. It is sealed in sterile rubber-capped bottles for use.

Recently another method of making vaccines has come into prominence, mainly from the work of the U. S. Army Medical School in Washington. The bacteria are suspended in cotton-seed oil and lanolin, after being ground in a mill for four hours. Such a product is called a lipo-vaccine, and it is claimed by Fennell* that the oil vehicle enables them to give larger doses with less reaction to the patient, and in this way the equivalent of the usual three typhoid inoculations may be given in one injection. The resulting immunity is said to be equal, if not superior, to that produced by the saline vaccines. This lipo-vaccine is now standard for use in the U. S. Army, against typhoid and the two paratyphoid organisms, making a triple lipo-vaccine. Pneumo-

* For preparation and discussion of lipo-vaccine, see Whitmore, Fennell, and Petersen, "An Experimental Investigation of Lipo-vaccine." *Jour. Am. Med. Assn.*, Feb. 16, 1918, **lx**, No. 7, 428.

coccus lipo-vaccine is also being used in the same forces as an optional measure.

In Koch's old tuberculins the essential point is the introduction of the extract of tubercle bacilli, as contained in the glycerin broth filtrate of a culture. In the case of more soluble bacteria autolysis is allowed to proceed either by heating in saline solution or in alkaline broth. The former method is employed by Hektoen and Rosenow²² in making their pneumococcus antigen. Other methods of obtaining bacterial extracts for immunization purposes include mechanical shaking in salt solution, trituration with sand, or with freezing, digestion with proteolytic enzymes, or extraction by pressure in a Buchner press. In the case of pneumococci, Neufeld dissolved the organisms in bile.

Finally there is the active immunization by *inoculation with bacterial products* (toxins). As a matter of fact, this method is only of value in connection with exotoxins, as in the case of diphtheria, tetanus, etc. With the discovery of such an exotoxin in the cultures of diphtheria bacilli, by Roux and Yersin,²³ the way was opened for the experimental immunization of animals against such soluble toxin. It is true that Salmon and Smith²⁴ had this idea in mind in immunizing pigeons against the bacillus of hog cholera in 1884, but as a matter of fact what they really obtained was antibacterial, and not antitoxic immunity. Brieger and Fraenkel,²⁵ and Behring,²⁶ with his coadjutors, who led the way in this field, succeeded in producing antitoxins in animals against the toxins of diphtheria and tetanus, and this has since been accomplished in the case of *Bacillus botulinus*, *Bacillus pyocyaneus*, and the bacillus of symptomatic anthrax. Recently Bull²⁷ succeeded in demonstrating a soluble toxin in broth cultures of *Bacillus aerogenes capsulatus*, and in producing a specific antitoxin for this infection. The importance of antitoxin immunization depends almost wholly upon the success which was found to attend the curative use of such antitoxic serum. In other words it was shown by v. Behring and Kitasato (*loc. cit.*) that animals inoculated with a lethal dose of toxin were protected by the injection of serum from other animals actively immunized against toxin. Thus the former animals were *passively* immunized. To quote these authors: "The blood of tetanus-immune rabbits possesses tetanus poison-destroying properties; these properties are demonstrable in the extravascular blood and in the serum obtained from this; these properties are of so lasting a nature that they remain active in the bodies of other animals, so that one is able to obtain positive therapeutic results by transfusing the blood or injecting the serum. These tetanus poison-destroying properties are absent from the blood of non-immune animals, and when the tetanus toxin is inoculated into normal animals it can be demonstrated as such in the blood and other fluids of these animals after death."

PASSIVE IMMUNITY.—It is quite evident from what has been already said that an attempt at active immunization would prove of no value to a patient if inaugurated during the course of an acute disease, as, for example, in diphtheria. It is easily seen that if the body cells

the host are to be artificially stimulated to produce the specific antibodies effect an immunity, the process will necessarily occupy an appreciable length of time—several days at least. As a matter of fact, it has been found by actual experience that before the antibodies can be produced in this way, in sufficient quantity to favorably alter the course of the disease, the patient has either recovered from the infection or has succumbed. Active immunization, therefore, probably finds its only satisfactory application in the field of prophylaxis, and in certain chronic infections. The term prophylaxis is here taken to include diseases such as rabies, in which sufficient time elapses between the time of infection and the onset of symptoms (incubation period) to allow of active immunization.

Early observers soon saw that for therapeutic use, therefore, they must look for some method of rapidly conferring immunity upon a patient already suffering from a disease. As early as 1890 and 1892, v. Behring and Kitasato²⁸ found that the serum of an animal immunized against tetanus toxin would, when inoculated into a normal animal, protect it against a lethal dose of toxin. It is obvious that here the protected animal takes no active part in producing its own immunity, and merely plays a passive rôle. The protective substances are furnished to the individual "ready-made," as it were. His cells have no part in their production, and the immune bodies must be introduced into the circulation artificially or through the placental circulation or milk of the immune mother to the susceptible offspring. Such a resistance to infection is termed *passive immunity* and can be conferred upon a susceptible animal so rapidly as to prove of great therapeutic value. It is highly specific.

It was found, however, that passive immunity can only be obtained by using the serum from an animal which has been immunized against the exotoxin of a given bacterium, or one which produces powerful endotoxin. Hence nearly all those microörganisms which depend for their pathogenicity upon the endotoxins, or toxic products, contained within their bacterial bodies, are unsuitable for this purpose. The bacteria which are true toxin-producers are comparatively few in number. They include *Bacillus diphtheriae*, *Bacillus tetani*, *Bacillus botulinus*, *Bacillus aerogenes capsulatus*, and possibly *Bacillus pyocyaneus*. Recent work by Clark and Felton²⁹ claims to show the presence of a filtrable toxic product from cultures of hemolytic streptococci. It is possible that as our knowledge of bacterial poisons advances, others may be added to this group. On the other hand, however, we have a comparatively potent serum against Type I pneumococcus, which so far as we know at present is antibacterial rather than antitoxic. The antidyenteric serum used with some success in the British Army Hospitals in the near East during the War depends for its curative action primarily upon its antitoxic, and secondarily upon its antibacterial properties, according to Graham.³⁰ It is claimed, however, that the antitoxic content is low, and that therefore large amounts must be used. Antibacterial serum, such as that against the meningococcus, is of value where

the serum may be brought into direct contact with the bacteria in a closed cavity, as the spinal canal; with this exception their use, while encouraging in experimental infections in laboratory animals, has not been of much therapeutic value in human disease.

Passive immunity, obviously, is not so lasting as the active type. Foreign proteins are more or less rapidly excreted from the body, and with them the antibodies for which the serum is administered. On the other hand, in active immunity, the cells of the body, and particularly those at the site of inoculation, as in artificial immunization, are actively engaged in antibody-production, and as a result a new supply of antibodies is constantly forthcoming to replace that excreted or neutralized.

MECHANISM OF THE PRODUCTION OF ACQUIRED IMMUNITY.—The inoculation of an animal or person with an antigen, either artificially or by infection with the organism in question, causes the cells of the body to react against the foreign material. This reaction is evidenced, so far as present methods are able to detect, by the presence in the circulating blood and tissue fluids, of certain immune bodies. These antibodies alone, and in conjunction with the leukocytes, tend to neutralize or destroy the antigen, and in this way produce an immunity. Thus the cellular and humoral theories of Metchnikoff and of Ehrlich, respectively, are together necessary to explain the mechanism. Metchnikoff's phagocytic theory did not at first recognize the importance of the coöperation of the antibody called opsonin, but with that essential addition, it stands as a fundamental contributory factor in both natural and acquired resistance. On the other hand, Ehrlich's side-chain theory has not been substantiated in its entirety, and probably never can be, but it is equally true that it has never been disproved, and whatever else is said, it must be admitted by every one that it furnishes a graphic and useful means of visualizing the phenomena which we do know take place, and with which his theory is in harmony.

True toxins, as has been mentioned before, acting as antigens, call forth *antitoxins*. These antibodies exert a simple neutralizing action upon their specific antigen, and in this manner render it innocuous. Antigens composed of bacterial or other cells, as red blood-cells, excite the production of various antibodies. Among these, *cytolysins* are important. In conjunction with complement they accomplish the solution of the antigenic cells. Where the latter happen to be bacterial cells the immune bodies are called *bacteriolysins*. The same type of antigen also calls forth *agglutinins*, which have the ability to clump the bacteria composing the antigen. Where the antigen is soluble, *precipitins* are produced in place of agglutinins. They manifest themselves by their power of causing a precipitation of the proteins of the antigen. The peculiar properties of these various antibodies, and their application to immunity and to serology, will be discussed in the sections devoted to that purpose.

These immune bodies are specific for their antigens. That is to say, the antitoxin produced in response to the inoculation of diphtheria toxin

will neutralize no other toxin. The agglutinins called forth by the presence in the body of typhoid bacilli will not agglutinate pneumococci, and vice versa. This idea of specificity was not fully appreciated until the work of Roux and Yersin, and of Kitasato on true bacterial poisons, as opposed to unspecific poisons or ptomains. Since that time, however, the multitude of observations, recorded and unrecorded, have left no doubt as to this question, and the specificity of immunity is one of the most important factors underlying serological tests and serum therapy.

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TOXIN AND ANTITOXIN

Experiments show that toxins are soluble in water and slowly dialyzable through thin membranes. They are uncrystallizable, differing in this way from the ptomains. They are precipitated along with peptones by alcohol, and by ammonium sulphate; they resemble albumoses to a considerable extent in their reactions. Heat and cold diminish or destroy their toxicity. Their potency is also diminished by the addition

of iodinterchlorid * and of other chemicals. They are highly specific in their action, both in animals and in the test-tube. In the former, they tend to attack certain types of cells, possibly because of chemical affinities, and thus give rise to characteristic symptoms. All true toxins have the power, when injected into the animal body, of exciting the production of specific antitoxins and in the test-tube as well, as in the body these antibodies counteract or neutralize the effect of the toxin.

Antitoxins are also precipitated by ammonium sulphate, coming down with the globulin fraction of the serum. Park and Atkinson¹ and Pick² have shown that the globulin precipitate carries with it all the antitoxic power of the serum, and that the filtrate contains no protective substances. Atkinson has also shown that the globulins in a horse which is being immunized are greatly increased as the process goes on. From these observations it is apparent that antitoxin is either a protein substance closely related to serum globulins or it is very closely bound to the globulins in the blood stream. Gibson and Banzhaf³ showed further that the globulins, which are insoluble in saturated sodium chlorid solution, carry with them no antitoxin. Based on these observations, the concentration of antitoxin is now successfully carried out in an economical manner, and has proved a great advantage both in the supplying and administration of large amounts to patients. Antitoxin is relatively thermostabile, being unimpaired by heating to 56° C. for a considerable period.

The Nature of the Toxin-antitoxin Reaction.—Since the exact chemical nature of toxins and antitoxins is unknown, and since neither has been obtained in a pure form, it is impossible to investigate the exact nature of their union with each other, as one would with substances like NaOH and HCl. The only way in which we can secure the necessary information is by animal experiment. In other words, it is impossible to say when a mixture of toxin and antitoxin is "saturated" or neutralized, save by inoculating suitable animals and by observing the effect.

The early workers, in casting about for an explanation of the reaction of antitoxin with toxin, naturally first thought that the process was one in which the destruction of the toxin was accomplished. That this was not the case was conclusively shown by Calmette,⁴ who worked with cobra venom as a toxin. This toxin was shown to be thermostabile, resisting a temperature of 100° C. for a short time. On the other hand, antivenin is relatively thermolabile. Calmette mixed the poison with its antitoxin in such quantities that the effect of the mixture was negligible. On being heated, however, the mixture became toxic, showing that after the heat had destroyed the antivenin, the toxin was freed, and retained or resumed its former characteristics. In short, it was not injured but simply bound by the antitoxin. Wassermann⁵ showed that the same held true for the toxin of *Bacillus pyocyaneus* and its antitoxin.

* Behring advised the use of iodinterchlorid to reduce the toxicity of the first few inoculations, in immunizing animals against diphtheria toxin.

That the toxin-antitoxin combination was in the nature of a chemical union was the belief of various workers and this conviction was strengthened by Calmette's observations, in which it was shown that if a sufficient time was allowed to elapse after the mixture was made, the toxic effect could not be produced by heating. This emphasizes the importance of the element of time, and supports the chemical nature of the union. Martin and Cherry⁶ similarly showed the importance of time in the reaction by filtering mixtures of toxin and antitoxin through fine filters. The pores of the filters were of such a size as to permit the escape of small molecules such as that of the toxin, whereas the larger antitoxin molecule was held back. They found that if they filtered the mixture directly after it was made, most of the toxin was obtained in the filtrate. If, however, they allowed the mixture to stand, after mixing, less of the toxin was recovered after filtering, and after two hours no toxin whatever was found in the filtrate. It was therefore thought probable that the toxin-antitoxin combination is a chemical one, requiring time for its completion.

The view that the combination is of a chemical nature received further support by the demonstration by Ehrlich⁷ in test-tube experiments, that the reaction followed roughly the law of multiple proportions, and was accelerated by heat, and by using the reagents in a concentrated form.

This work was done by Ehrlich upon ricin, the poisonous element of the castor-bean, which has the power of agglutinating red blood-cells. Neutralization of the ricin with antiricin, previous to mixing with red blood-cells, results in preventing agglutination. Here Ehrlich found a method of determining the results of his neutralization experiments *in vitro*, without recourse to animal tests. These visible results were afterwards confirmed, however, by the inoculation of animals. The close resemblance to known chemical reactions was evident from the experiment, in which he set up a series of quantitatively graded mixtures of ricin and antiricin, using rabbits' red blood-cells as indicators. This experiment showed that definite quantitative relations existed between the two substances closely following the law of multiple proportions so well known in chemistry. Incidentally his experiments also showed conclusively that tissue cells have no part in the toxin-antitoxin reaction.

Ehrlich's observations on the relation of heat and cold to this reaction were confirmed by Knorr.⁸

In the case of diphtheria toxin, the union of the poison with the tissue-cell is not so firm as is the case with tetanus toxin. The longer the toxin is in contact with the cell, however, the firmer is the union. It is important, therefore, in using antitoxin as a therapeutic measure, that the administration be performed at the earliest possible moment. The dose should be large enough to neutralize all free toxin as well as that which is loosely bound, with an ample excess, to deal with toxin, being prepared by the microorganisms at the site of infection.

With the establishment of the therapeutic value of diphtheria and tetanus antitoxin, and especially after Ehrlich had demonstrated the

facts concerning the quantitative relations between toxin and antitoxin. Behring decided that any work upon these substances should be based upon a standard toxin unit which, in the case of diphtheria, he arbitrarily set as *that amount of toxin sufficient to cause the death of a guinea pig of 250 grams weight in four days*. This unit is called the M.L.D. (*minima dosis lethalis*).

In collaboration with Ehrlich, Behring then set the standard of antitoxin. This has undergone certain alterations, and now the unit stands as *the quantity of antitoxin which completely neutralizes 100 M.L.D. of toxin*. This standard has been adopted the world over. Since toxin deteriorates much more rapidly than antitoxin, the latter has been preserved as the government standard. In order that all workers should be provided with identically the same standards, the various governments have provided antitoxin which has been desiccated and kept in powder form. Stored in the dark, in a cool atmosphere, it may be kept for long periods of time without appreciable deterioration.

As stated above, toxin is much more unstable, and this led to important observations by Ehrlich. He established the amount of toxin which was just neutralized by one antitoxic unit, and called this L_0 (L meaning Limes, or threshold). He then established the amount of toxin which, besides neutralizing one unit of antitoxin, contained enough toxin to kill a 250-gram guinea pig in 4 days. This toxin value he called L_4 , and in determining the strength of toxic filtrates it is found to be a much more accurate means than L_0 , since it allows of less variation to estimate the quantity of toxin just required to kill than to estimate the quantity which just neutralizes one unit of antitoxin.

To summarize, then, we may state that:

M.L.D. = the amount of toxin which just kills a guinea pig of 250 grams in about 4 days.

L_0 = the amount of toxin which just neutralizes one unit of antitoxin.

L_4 = the amount of toxin which, besides neutralizing one antitoxin unit, leaves enough free toxin to kill a 250-gram guinea pig in about 4 days.

The titrations for arriving at these amounts of toxin are accomplished by injecting several guinea pigs subcutaneously with varying quantities of the toxic filtrate which is being examined, or in the cases of L_0 and L_4 by injecting it together with a constant quantity of antitoxin (1 unit).

In making these titrations in a large series of toxic filtrates, Ehrlich observed that the same toxin would deteriorate very rapidly as regards toxicity, so that the M.L.D. and L_4 doses would become larger and larger as time went on, while the neutralizing power of the toxin, i.e., the L_0 dose, remained the same. After extensive experiments he concluded that the haptophore group of the toxin molecule (*see* Ehrlich's side-chain theory, page 224) remains the same, but that the toxophore group becomes altered on standing for a time, this altered toxin being less potent as regards toxicity. These deteriorated toxin molecules were

termed **toxoids**. By this ingenious explanation, it is easily seen, therefore, how the presence of toxoids in a toxic filtrate would not change the neutralizing power (the L_0 dose), but would increase the amount necessary to kill, whether it be the M.L.D. or the L_0 dose. These observations of Ehrlich have been confirmed by many observers until, at the present time, toxins used in the actual immunization of horses for therapeutic purposes are allowed to stand for a time until the deterioration has reached a more or less stationary point. In this way a much greater uniformity is attained.

Another apparent paradox was soon discovered by Ehrlich. He naturally expected that in spite of the deterioration of the toxic molecule into toxoids, the difference in the values of L_0 and L of any given toxin at any given time would be equal to one toxic unit, or one M.L.D. As a matter of fact, he found that it amounted to many times what would be expected. The following protocol, taken from Ehrlich's work, illustrates this point:

M.L.D. = 0.01 c.c. of the toxic filtrate,
 L_0 = 2.01 c.c. or 201 M.L.D.
 L_0 = 1.0 c.c. or 100 M.L.D.

Difference = 1.01 c.c. or 101 M.L.D. instead of 1 M.L.D., as might be expected.

To explain this curious fact, Ehrlich was forced to believe that toxins, or certain portions of toxic filtrates, vary in their combining affinity for antitoxin. This is an important principle in his explanations of serum reactions. At first he thought that certain of the toxoids might possess a weaker affinity for antitoxin. These he called epitoxoids. Later he discovered that what he had called epitoxoids were present from the very beginning in the toxic broth, before any deterioration into toxoid could take place, and were probably primary secretory products of the micro-organisms, just as in toxin. This conception was confirmed by later experience, and this second product was named *toxon*. These toxons possess a combining or haptophore group similar to toxins, but the toxophore group is quite different. This we shall discuss later. The toxons possess a weaker affinity for antitoxin than do toxin molecules. Hence if we have a hypothetical mixture of toxin molecules and antitoxin molecules which are exactly neutralized (L_0), the results in a guinea pig would be negative. As a matter of fact, however, all mixtures of toxic broth which completely neutralize antitoxin must contain toxin-antitoxin molecules and toxon-antitoxin molecules.

If to such a mixture we should add one toxin molecule which has a greater affinity for antitoxin than toxon, one toxon-antitoxin molecule would be dissociated and the toxin molecule would unite with the freed antitoxin molecule. This would leave one toxon molecule free. In the same way if we should add another toxin molecule there would be two free toxons. If we should add as many toxins as there were toxons in

the original mixture, all the toxons would be free. If still another toxin is added, it remains free and the resultant mixture becomes toxic to the guinea pig. This is well illustrated by a further quotation from Ehrlich's work, and is an example of his "partial saturation" experiments:

$$100 \text{ toxin-antitoxin} + 100 \text{ toxon-antitoxin} = L_0$$

Add 1 toxin unit (M.L.D.) and we have:

$$101 \text{ toxin-antitoxin} + 99 \text{ toxon-antitoxin} + 1 \text{ toxon free.}$$

Or add 100 toxin units and we have:

$$200 \text{ toxin-antitoxin} + 100 \text{ toxon free.}$$

Now if we add 1 toxin unit we have:

$$200 \text{ toxin-antitoxin} + 100 \text{ toxon free} + 1 \text{ toxin unit free} = L_1.$$

So we see that the apparent discrepancy between the L_0 dose and the L_1 dose is due to the presence of toxons in the toxic broth. These toxons are of use in neutralizing antitoxin, and therefore are of service in making up the L_0 mixture. They are not toxic, however, in the same sense as toxin, and therefore are inert as regards the L_1 dose. Nevertheless, in making up the latter, enough toxin must be used to first displace all the toxon from its weak union with antitoxin, before any free toxin will be available to kill the guinea pig.

What, then, are the properties of toxons? It was observed that they lack the power to produce acute death, but that they do cause emaciation and paralysis. That is, in the above example of Ehrlich's:

$$L_0 = 100 \text{ toxin-antitoxin} + 100 \text{ toxon-antitoxin} = \text{no effect on guinea pig.}$$

$$200 \text{ toxin-antitoxin} + 100 \text{ toxon free} = \text{slow emaciation and paralysis, and eventual death.}$$

$$L_1 = 200 \text{ toxin-antitoxin} + 100 \text{ toxon free} + 1 \text{ toxin free} = \text{acute death in 4 days.}$$

The effect of these toxons is often seen in cases of diphtheria with so-called late paralysis of palatal muscles and vagus involvement. Ehrlich's conception of toxon was further supported by Dreyer and Madsen,⁹ who showed by actual experiment that the deductions regarding the action of mixtures so balanced as to possess free toxon but no free toxin were correct. Injection of these mixtures possessing free toxon produced immunity to toxin (antitoxin), thus proving Ehrlich's contention that the haptophore group of the toxon molecule is identical with that of the toxin molecule.

Thus we have three distinct elements in the toxic broth:

1. **Toxin**:—present as a primary excretory product of the bacteria; produces acute death.
2. **Toxon**:—present as a primary excretory product; produces slow emaciation and paralysis.
3. **Toxoid**:—derived from toxin by deterioration; not excreted by the bacteria as toxoid.

These elements possess one thing in common—a similar haptophore or combining group. They differ in the toxophore group only. Therefore the antibody they call forth, when used as an antigen, is similar, i.e., antitoxin. These fundamental facts influence, as we shall see, the modern methods of producing antitoxin for therapeutic use.

Before leaving the subject of the nature of the toxin-antitoxin union, it may be well to mention another point regarding the present conception of this phenomenon. This is the "absorption theory" of Bordet. He believes that when toxin is mixed with antitoxin in amounts not sufficient to neutralize completely the former, the antitoxin molecules do not completely saturate or neutralize the toxin molecules until all the antitoxin is used up, thus leaving a certain amount of free toxin. On the other hand, he and his followers believe that each molecule of toxin in such a mixture is only partially saturated, and thus an attenuation of the toxin is accomplished.

The following list of antitoxins is adapted from Wassermann:

I. Antitoxins for bacterial toxins.

- Diphtheria antitoxin.
- Tetanus antitoxin.
- Botulism antitoxin.
- Pyocyaneus antitoxin.
- Symptomatic anthrax antitoxin.
- Bacillus aerogenes capsulatus* antitoxin.
- Dysentery antitoxin (Shiga-Kruse).
- Antileukocidin, an antitoxin for the leukocytic poison of the *staphylococcus*.
- Antitoxins for the blood-dissolving toxins of a number of bacteria.

II. Antitoxins for animal toxins.

- Antivenin for snake poison.
- Antitoxin for scorpion poison.
- Antitoxins for spider poison, and wasp poison.
- Antitoxins for certain poisons of fish, eel serum, salamander, and turtle.

III. Antitoxins for plant toxins.

- Antiricin for a poison of the castor oil bean.
- Antiabrin, for a poison of the jequirity bean.
- Antirobin, for robin, a locust tree poison.
- Antierotin, for erotin, of the croton oil bean.

IV. Antiferments.

Antirennet.

Antipepsin.

Antitrypsin.

Antifibrin ferment.

Antiurcase, for urease, a urea splitting ferment.

Antisteapsin.

Antiferments for the ferments of bacterial cultures.

The Production of Antitoxin for Therapeutic Use.—Park¹⁰ gives the following directions regarding the methods in use in the laboratories of the Health Department of New York City:

A strong diphtheria or tetanus toxin should be obtained by taking a very virulent culture and growing it in broth. The following directions apply to the production of diphtheria antitoxin:

The horses used should be young, vigorous, of fair size, and absolutely healthy. They are severally injected with 10,000 units of antitoxin, so as to allow for giving them a much larger dose of toxin than would otherwise be safe. This means a gain of several weeks in time. The following figures give the actual injections in a horse which produced an unusually high grade of serum.

An injection was first given of 10,000 units of diphtheria antitoxin. Injections of toxin were given at first every two days, and then later every three days in the following amounts:

First day, 12 c.c. toxin (0.0025 c.c. fatal dose).

Second and later injections of toxin without antitoxin at three-day intervals as follows: 15 c.c., 20 c.c., 30 c.c., 40 c.c., 50 c.c., 60 c.c., 80 c.c., 100 c.c., 125 c.c., 150 c.c., 170 c.c., 205 c.c., 250 c.c., 300 c.c. (fortieth day). The injections were gradually increased until on the sixtieth day 675 c.c. were given. The whole injection was not in one place, but divided into six or eight portions.

The antitoxic strength of the serum was: on the twenty-eighth day 225 units, on the fortieth day 850 units, and on the sixtieth day 1,000 units. Regular bleedings were made weekly for the next four months, when the serum had fallen to 600 units in spite of weekly, gradually increasing, doses of toxin.

The technic for the production of tetanus antitoxin is the same, excepting that more caution is required, and a slower increase is attempted.

After the antitoxic titer of the horse's serum is satisfactorily high, bleeding is done into cylindrical jars containing sodium citrate, to prevent clotting. The citrated plasma is mixed with saturated ammonium sulphate so as to produce a 30 per cent. solution. The whole is heated to 60° C. for one hour, and filtered while hot. The filtrate is raised to 50 per cent. saturated ammonium sulphate solution. The precipitate (containing the pseudoglobulins along with the antitoxin) is pressed to remove excess fluid (this step is very important), and dialyzed until

free from salts. The precipitate is by this time dissolved in the fluid which has entered the dialyzing bag and 0.3 trikresol is added to preserve the sterility. It is then passed through a Berkfeld filter, sealed in vials, and is ready for use, after standardization. Samples are cultured to test the sterility.

To standardize the antitoxin, all laboratories must have a uniform basis upon which to proceed. Antitoxin is measured in terms of toxin, and consequently this requires the proper standardization of the toxin used. Antitoxin is more stable than toxin, and for this reason it is supplied to the various laboratories by the Hygienic Laboratory at Washington, where it is kept preserved in powdered form over anhydrous phosphoric acid in sealed tubes. The toxin is titrated against this standard antitoxin, and the L_1 dose ascertained. This dose is the amount of toxin which will not only neutralize one unit of antitoxin, but also will provide enough toxin to kill a 250-gram guinea pig in four days. This assures a much more definite end-point than that of estimating the L_0 dose of toxin.

Having thus determined the L_1 dose of toxin, this amount is mixed with varying quantities of the unknown antitoxin. The concentrated antitoxin will probably contain 1,000 or more units per c.c. Thus, the L_1 dose of toxin is mixed with one c.c. of the following dilutions of unknown antitoxin: 1:500; 1:600; 1:700, etc., and these mixtures are injected subcutaneously into guinea pigs weighing 250 grams. The mixed toxin and antitoxin must remain together for at least fifteen minutes before injection to allow complete union to occur (Park).

The following protocol will illustrate the test:

Injectations of toxin-antitoxin mixtures:

- (1) L_1 dose of toxin + 0.0004 c.c. unknown antitoxin death in 1 day.
- (2) L_1 dose of toxin + 0.0006 c.c. unknown antitoxin death in 2 days.
- (3) L_1 dose of toxin + 0.0008 c.c. unknown antitoxin death in 3 days.
- (4) L_1 dose of toxin + 0.001 c.c. unknown antitoxin dies on 5th day.
- (5) L_1 dose of toxin + 0.0012 c.c. unknown antitoxin living after 5 days.
- (6) L_1 dose of toxin + 0.0014 c.c. unknown antitoxin living after 5 days.

In the above experiment, guinea pig No. 4 must have received at least one unit of antitoxin. (We must discard Behring's old definition of a unit of antitoxin, which holds true only if we are using normal toxins and antitoxins as at first devised by him. Under present methods of standardization, a unit of antitoxin may be said to be that amount of antitoxin which protects a 250-gram guinea pig for four days against an L_1 dose of toxin.) The unknown antitoxin therefore contains in each c.c. at least 1000 units of antitoxin, but less than 1250 units, since 0.0008 c.c. $\left(\frac{8}{10,000}$ c.c.) failed to protect. Another series of guinea pigs are then injected with amounts ranging between these points, in order to ascertain more accurately the exact antitoxic content.

Tetanus antitoxin is tested in exactly the same manner as in diphtheria, except that the serum is tested against 1000 fatal doses of tetanus antitoxin, instead of 100 fatal doses as in diphtheria toxin.

Antitoxin for use in diphtheria is used therapeutically in doses ranging from 5000 units to 100,000 units, or even more. The prophylactic dose is from 500 to 1000 units. In tetanus, the therapeutic dose is 5000 to 20,000 units, and the prophylactic dose about 1500 units.

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AGGLUTININS AND PRECIPITINS

In the previous sections we have been discussing the nature of immune bodies of the first order, according to Ehrlich's side-chain theory. We now come to a consideration of the receptors or antibodies of the second order. These include agglutinins and precipitins. These immune substances differ from those of the first order in that they are more complex since they possess, besides a haptophore or combining group (as in those of the first order), a second or *zymophore* group, by means of which the anchored antigen may be subjected to further change.

Agglutinins.—These receptors are produced in response to antigens composed of bacterial cells, red blood-cells and certain protozoa (as trypanosomes). (Gruber and Durham,¹ following the observations of various workers before them, called attention to the action of homologous immune serum upon bacterial antigens. Upon bringing a broth culture of colon bacilli into contact with the serum of a guinea pig which had previously been immunized by injections of these microorganisms, it was observed that the culture medium lost its turbidity, and that flakes or clumps were formed which rapidly settled to the bottom of the tube. These clumps were found to be composed of clusters of bacilli, which had apparently adhered to each other.

These workers recognized that this phenomenon did not occur when bacteria of other types were subjected to the influence of colon-immune serum. In other words, the reaction was found to be specific. True enough, they did observe that there was a "group reaction," inasmuch

as the serum of a colon-immune animal could cause a moderate agglutination in cultures of microorganisms allied to the colon bacillus, such as the typhoid bacilli. Nevertheless, the specificity was of such a high order that the specific antigen was found to be agglutinated by much greater dilutions of the serum than any emulsions of even closely allied types of bacteria. Widal, soon after, applied the knowledge thus obtained to the diagnosis of typhoid fever. He found that the serum of patients suffering from this disease contained agglutinins which were highly specific for the typhoid bacillus, and that by bringing a drop of such serum into contact with a drop of a broth culture of *Bacillus typhosus*, he could observe the agglutination actually occurring under the microscope. It was soon found that the converse of these reactions also took place. In other words, given a serum immune to a certain type of microorganism, it could be used to determine the identity of an unknown culture. Thus if we wish to determine the nature of an unknown bacillus suspected of belonging to the typhoid bacillus group, we may bring it into contact with a known typhoid-immune serum. If it is agglutinated, we can say definitely that it is the typhoid bacillus; if it is not agglutinated, we may try it out with sera immune to other microorganisms, until its identity is established.

The principle here involved has had a very wide application, not only in the identification of various species of bacteria, especially those of the colon-typhoid-dysentery group, but also in determining various types of the same species. Thus Cole, and his associates,² as well as Lister,³ have succeeded by this method in discovering several types of pneumococci, and Shiga in a similar manner discovered the particular type of dysentery bacillus which bears his name.

There are two methods of performing the agglutination tests, the microscopic and the macroscopic. For the microscopic method, very little blood is needed, and it may be secured by pricking the patient's ear or finger, and drawing the blood into a Wright capillary capsule, in which the serum is separated by standing or by centrifuge. Blood to be sent to laboratories of various Boards of Health from a distance may be allowed to dry on a piece of glazed paper, or on a ground-glass slide.

For the macroscopic method, more blood is needed, and is readily obtained by puncturing the vein at the bend of the elbow with a hypodermic needle attached to a 1 c.c. syringe, and transferring the blood to a narrow test-tube which may be placed in a centrifuge to facilitate the separation of the serum. Indeed, this procedure is so simple and so effective that the author adheres to it even when desiring to use the microscopic method only.

A. MICROSCOPIC AGGLUTINATION TEST.—1. The serum is diluted 1:20 with a normal saline solution. This may be accomplished by placing a drop of serum on a watch-glass and adding 19 drops of saline solution. A very convenient method is to use the white cell pipet of a hemocytometer outfit, drawing the serum to the mark 0.5, then saline to the 11 mark. Shake and expel the mixture onto a watch-glass or glass slide.

2. With a 4 mm. platinum loop place a drop of the 1:20 dilution of serum near the center of a clean cover-slip.

3. Using the same platinum loop (sterilized in a bunsen flame), place a similar drop of a twenty-four-hour culture of *B. typhosus* grown at room temperature, beside the drop of saline on the cover-slip.

4. Mix gently without spreading the drop too widely. This gives a 1:40 dilution.

5. Invert a hanging-drop slide, the vulcanite ring of which has previously been greased with vaselin, over the cover-slip and turn right side up so that the drop will hang suspended in the center of the vulcanite ring. The vaselin will hold the cover-glass securely in place, and will prevent evaporation during the test.

6. Prepare a second slide in the same way, only this time instead of diluted serum, use saline solution. This is the *control*.

These preparations are now allowed to stand at room temperature for half an hour, at the end of which time the control slide should be examined under the high dry lens of a microscope. The bacilli should be uniformly distributed about the field, and should exhibit active motility. Now examine the test slide in the same way. A positive reaction is indicated by loss of motility and definite clumping. A few free bacilli are sometimes seen, and occasionally these are motile, but the overwhelming number are agglutinated and motionless. A *doubtful* reaction is indicated by partial loss of motility and a few indefinite clumps. A *negative* reaction is indicated by an appearance identical with the control.

B. MACROSCOPIC AGGLUTINATION TEST (Dreyer Method *).—The culture of *B. typhosus*, *B. paratyphosus*, or *B. coli* to be used should be inoculated into plain broth and incubated at 37° C. for from twenty-two to twenty-four hours. They are then well shaken up and 0.1 per cent. of the ordinary 40 per cent. solution of formalin is added. Shake again that day and on the following days. The cultures are sterile after seventy-two hours. They may then be filtered through sterilized, coarse, filter paper, if not entirely homogeneous, and put into sterilized bottles with rubber corks, or vaccine caps, and kept in the cold and dark.

1. Place a row of ten small test-tubes in a rack, and add 1 c.c. of physiologic saline solution to each.

2. In the first tube place 0.2 c.c. serum and 0.8 c.c. saline solution; mix well. This now gives 2 c.c. of a dilution of 1:10.

3. Place 1 c.c. from Tube 1 into Tube 2. Mix well and place 1 c.c. from Tube 2 into Tube 3, and so on. When the ninth tube has been reached, discard 1 c.c., as no serum is to be placed in Tube 10, which is the culture control, and will contain only saline solution and bacterial emulsion.

4. Add 1 c.c. of sterilized culture emulsion to each tube. This doubles the dilution so that we have a series of tubes containing the following dilutions of serum: 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1280, 1:2560, and 1:5120. The tenth tube, as just stated, contains only culture emulsion and saline solution.

5. Each tube is shaken thoroughly and the rack is placed in the thermostat at 37° for two hours, or at room temperature for twenty-four hours, when they are examined.

If a measurable amount of agglutinin is contained in the serum, one or more of the tubes will have become clarified, and less opalescent. A light flocculent deposit will be found at the bottom of such tubes, while the control tube will remain diffusely turbid.

A positive result in Tube 1 (1:20) only must be regarded as a doubtful reaction, and such serum should be tested again a few days later, as some normal sera give rise to agglutination at this dilution. Well marked agglutination in dilutions of 1:40 or over may be taken as definitely diagnostic of active typhoid (or paratyphoid) infection.

C. AGGLUTINATION TESTS FOR DETERMINATION OF TYPES OF PNEUMOCOCCUS.—Since the researches of Dochez and Gillespie,⁵ Avery and Dochez,⁶ and Lister⁷ on the biologic and serologic classification of pneumococci it has become a common practice to determine the types of the infecting pneumococcus in cases of lobar pneumonia, with a view to a more intelligent use of the therapeutic serum available for Type 1 cases. The following description of the test is based largely on the method given in the monograph issued by the Rockefeller Institute for Medical Research upon this subject in October, 1917:

A small portion of the sputum, about the size of a bean, is washed in sterile saline solution to remove surface contaminations. It is then transferred to a sterile mortar, ground up, emulsified in 1 c.c. of sterile broth or saline solution, and inoculated intraperitoneally into a white mouse. As soon as the mouse appears sick, a drop of peritoneal exudate is withdrawn by means of a capillary pipet, and examined by staining a film with Gram's stain. If an abundant growth of pneumococci is present, the mouse is killed and the peritoneal cavity is opened with sterile precautions. The peritoneal exudate is then washed out with a sterile saline solution, using a pipet to which is attached a rubber nipple. The emulsion is centrifuged at slow speed for a few minutes, to throw down cells and fibrin. The supernatant bacterial emulsion is then transferred to another tube, centrifuged at high speed, and the resulting sediment of bacterial bodies is suspended in a fresh saline solution. The concentration of bacteria should be similar to a good eighteen-hour broth culture of pneumococcus.

Five small test-tubes are set up as follows:

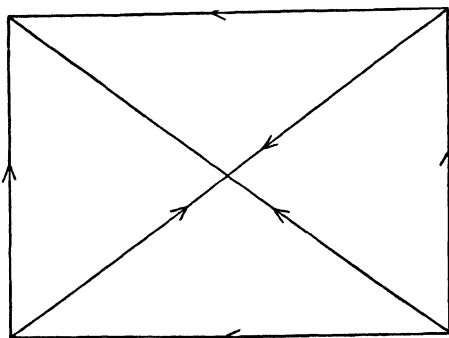
- Tube 1, 0.5 c.c. antipneumococcus serum Type I (1:20) + 0.5 c.c. bacterial suspension.
- Tube 2, 0.5 c.c. antipneumococcus serum Type II + 0.5 c.c. bacterial suspension.
- Tube 3, 0.5 c.c. antipneumococcus serum Type II (1:20) + 0.5 c.c. bacterial suspension.
- Tube 4, 0.5 c.c. antipneumococcus serum Type III (1:5) + 0.5 c.c. bacterial suspension.
- Tube 5, 0.1 c.c. sterile ox-bile + 0.4 c.c. bacterial suspension.

The tubes are incubated in the water-bath for 1 hour at 37° C. Agglutination occurs promptly in the case of Types I, II, and III, and is specific. If no agglutination occurs, and Tube 5 shows solution of the bacteria, the strain belongs to Type IV. Strains of atypical Type II pneumococcus will not be agglutinated by the 1:20 dilution of Type II serum, but will show partial agglutination in undiluted serum. If the emulsion fails to dissolve in bile, it is composed of streptococci.

D. AGGLUTINATION TEST FOR THE SELECTION OF DONORS FOR TRANSFUSION OF BLOOD.—It is some years since transfusion was first resorted to as a therapeutic measure. It was then thought to be of use only in emergency cases, and was not a common procedure. Recent simplification in technic has brought it into popular favor, and this form of

I (No agglutinin)
(10 per cent. of all persons)

III (1 agglutinin—"B")
(7 per cent. of all persons)



II (1 agglutinin—"A")
(40 per cent. of all persons)

IV (Both agglutinins—"A + B")
(43 per cent. of all persons)

FIG. 4.—AGGLUTINATION OF THE CORPUSCLES OF THE VARIOUS GROUPS BY THE SERUMS OF THE GROUPS FROM WHICH THE ARROWS LEAD. (After Sanford.)

therapy may now be utilized by any physician who is willing to acquaint himself with the principles involved, and the actual operative procedure. The obstacles in the way of transfusion at present are not difficulties in the operation itself, but fears arising from the knowledge that the selection of a donor is a matter of great importance, and that the results may be most disastrous if a weak, perhaps dying patient, is suddenly overwhelmed by the introduction into his veins of incompatible blood.

The researches of Landsteiner^{8,9} first drew attention to the action of the serum of one individual upon the corpuscles of another individual of the same species. It was found that the serum of one animal of a species agglutinates or hemolyzes the corpuscles of another animal of the same species. For this we have the term "iso"-agglutination, and "iso"-hemolysis. This is not auto-agglutination and autohemolysis, which latter terms would imply the agglutination or hemolysis of an animal's corpuscles by his own serum. Auto-agglutination probably never takes

place, according to Moss,¹⁰ but the same author suggests that autohemolysis takes place in instances of paroxysmal hemoglobinuria. Out of 213 cases investigated, autohemolysis was observed only once, and the author thinks that the hemolysis in that instance may have been due to extraneous causes. For all practical purposes, therefore, auto-agglutination and autohemolysis may be disregarded, and our attention confined to iso-agglutination and isohemolysis.

Landsteiner pointed out that human beings may be classified into groups, by studying the action of the serum of one person upon the corpuscles of another. He suggested three groups, A, B, C. Moss,¹⁰ in 1910, discovered that there were four groups, and his contention has been confirmed many times since, and is now accepted as fully established. The interrelation of the Moss agglutination groups is easily understood from the accompanying diagram (Fig. 4), taken from Sanford.¹¹

Five per cent. of all people belong to Group I. Group II comprises 42.5 per cent.; Group III, 9 per cent.; and Group IV, 43.5 per cent. These figures are approximate and based on the observations of Sanford¹² on 943 persons.

The following is a summary of the findings of Moss:

"It was learned that iso-agglutinins and isohemolysins appear with approximately the same relative frequency in health and in disease, and therefore have no diagnostic significance. In a number of healthy individuals whose blood was repeatedly tested at varying intervals of time, the agglutinating action was found not to vary, while in some instances the hemolytic action which was present in earlier tests was absent in subsequent tests. There are at least three different iso-agglutinins and three iso-hemolysins in human sera, and three different iso-agglutino-philic, and three isohemolysinophilic receptors possessed by human red blood-cells.

"There are human beings whose sera contain no iso-agglutinin and no isohemolysin, but whose corpuscles possess receptors for iso-agglutinin and isohemolysin.

"On the other hand, the corpuscles of a given individual may possess no iso-agglutininophilic or isohemolysinophilic receptors, or they may possess two or all three kinds of these receptors.

"The serum of members of any one group will not agglutinate or hemolyze the corpuscles of other members of the same group, but will agglutinate and may hemolyze the corpuscles of members of any other group except those of Group IV. This may have a practical application in the transfusion of blood from one individual to another.

"Iso-agglutination may occur independently of isohemolysis, but isohemolysis is probably always preceded or accompanied by iso-agglutination.

"All the sera investigated contained an antihemolysin which protected the homologous corpuscles and those of members of the same group from solution by any other serum.

"This antihemolysin is an anti-amboceptor which acts by uniting with

the cytophilic group of the hemolysin, thus blocking it off from the red blood-cell, and probably consists of receptor groups of the red blood-cells which have been cast off from the cells, or set free by the physiological or pathological destruction of the corpuscles.

"Iso-agglutinin and isohemolysin are thermostabile, that is, they resist heating to 55° C. for 30 minutes.

"The antihemolysin is thermostabile, resisting heating to 55° C. for 30 minutes.

"The origin of iso-agglutinin and isohemolysin has not yet been satisfactorily determined. It probably cannot be referred to the destruction and resorption by an individual of his own blood."

Tests made upon patient and donor after the transfusion is no criterion as to the relation of their blood before the operation, because it has been shown by Ottenberg¹³ that in many cases the agglutinin in the patient's serum is absorbed by the sudden presence of receptors of the donor's corpuscles. In other words, many cases in which the patient's serum shows agglutination of the donor's corpuscles would show no agglutination after the transfusion.

The question naturally arises as to the importance or necessity of performing the test before transfusions upon patients are attempted. A satisfactory basis upon which to answer this question would be to show that cases transfused from a donor with incompatible blood will exhibit untoward results. The evidence on this particular point is necessarily meager. The only authentic cases on record are those reported by Ottenberg in which two patients were transfused from donors whose serum agglutinated the patients' corpuscles, and two patients whose serum agglutinated the donors' corpuscles. In the former two cases excellent results were obtained. In the latter two, the following observations were made:

1. One patient showed no untoward symptoms. The other, six hours later, developed hemiplegia and coma and died in 9 hours.
2. Smears made from the blood of the patients after the transfusion showed active phagocytosis of red cells.
3. The serum of the patients no longer agglutinated the donors' corpuscles.

These two cases were evidently ones in which there was only a moderate amount of agglutinin in the patient's serum, and this was all absorbed by the donors' corpuscles. In the majority of cases, therefore, intravascular agglutination does not occur, or, if it does, causes no symptoms. This is dependent on three main factors:

1. Concentration of the agglutinin.
2. Absorption of the agglutinin by an excess of agglutinable cells.
3. Interference with agglutination by an excess of non-agglutinable cells, so that when clumps occur they are microscopic in size.

Intravascular agglutination can occur, however, and is the probable cause of occasional untoward symptoms, or even death, following the transfusion of agglutinative blood, as in the second case cited above. Agglutinable cells, when transfused, are taken up by the phagocytes in the patient's blood (Ottenberg) and, for this reason, the transfusion of agglutinable blood, even when no accident happens, can be expected to do little permanent good.

There are various methods used in the selection of donors, all of which have their own advantages. The original method is the macroscopic one, described by Moss, and by Grafe and Graham.¹⁴

This procedure, described in various texts (Bolduan, Kolmer, etc.), consists in mixing in a small test-tube a definite quantity of a suspension of washed corpuscles of the donor with twice the amount of the patient's serum, and also in a similar manner the donor's serum with the patient's corpuscles. These tubes of cells and serums are incubated for one hour, being examined every few minutes for signs of iso-agglutinins or iso-hemolysins. At the end of the hour, if no agglutination or hemolysis has occurred, the transfusion is usually done, though some men have advocated keeping the blood over night in an ice-box before concluding that there is no incompatibility. Even a slight trace of hemolysin in the patient's serum for the donor's corpuscles is objectionable. However, it is a fact to be remembered, that hemolysis does not occur unless it has been preceded by agglutination.

A modification of this method is a micromacroscopical method, using capillary tubes and small quantities of blood, as described by Ottenberg. This method is said to be more quickly completed than the preceding one.

The microscopical method can be performed accurately and with a great saving in time. Moss¹⁵ recently published a description of the method he is using. This necessitates the keeping on hand of serum of Groups 2 and 3. Hanging-drop preparations are made by mixing a drop of suspension of the cells of the individual of the unknown group with two drops of serum of Group 2; and another preparation is made using serum of Group 3. Agglutination with both serums places the unknown in Group 1. If the Group 2 serum agglutinates the corpuscles, the unknown is in Group 3, and if the corpuscles are agglutinated by Group 3 serum, the unknown is in Group 2. If no agglutination occurs after thirty minutes the unknown is in Group 4. The serums of the known groups may be preserved for a long time if kept sealed and sterile.

The method described by Brem¹⁶ in 1916 is also microscopical and very similar to the Moss method, differing in that the corpuscle-suspensions of known groups, as well as serums, are used.

The point is often raised by those who do only an occasional transfusion that it is not feasible to have at hand the necessary blood of known groups, and to go through the test as Brem has described it. This is true. However, it is a very simple matter to use Brem's method to determine whether a prospective donor's blood is suitable for the recipient,

and not really know to which group either individual belongs. The technic for such a test would be as follows:

From the patient collect from 1 to 2 c.c. of blood in a dry sterile test-tube, and allow this to clot and the serum to collect, either from standing or from being centrifugalized. In another small test-tube containing 1 c.c. of 2 per cent. sodium citrate make a suspension of corpuscles with two or three drops of the patient's blood. In like manner prepare a tube containing the donor's serum, and another of the donor's corpuscle-suspension. With a clean wire loop mix two drops of the patient's serum with one drop of the donor's corpuscles on a cover-slip, and then two drops of the donor's serum with one drop of the patient's corpuscles on another cover-slip. Make hanging-drop preparations by inverting over hollow-ground slides, and examine with the microscope. If, after waiting fifteen minutes there is no agglutination on either slide, it is evident that the donor and the patient are in the same group, and the operation may be performed. If the donor's serum agglutinates the patient's corpuscles, but there is no agglutination of the donor's corpuscles by the patient's serum, the transfusion may be safely done, even knowing that the donor is not in the same group as the patient. But if the patient's serum shows any agglutinin for the donor's corpuscles, then under no circumstances should that donor be used, but another individual should be selected for trial, and the test repeated. Except in actual emergency transfusions complement-deviation tests for syphilis should be made on the blood of donors.

Precipitins.—In 1897, while working with broth filtrates of *Bacillus pestis* and the spirillum of cholera, Kraus¹⁷ discovered that these filtrates when brought into contact with serum from animals immunized against them would become turbid. After standing a long time, a flocculent precipitate would form. He found that this reaction was specific, and could be applied to the filtrates of other bacteria. He called this phenomenon the "precipitin reaction," and the immune substances in the serum were named "precipitins."

Although Kraus made his observations entirely with bacterial filtrates as antigens, it was soon found that every soluble native protein would act as antigen and that the anti-sera obtained were highly specific. Thus Bordet¹⁸ was able to produce specific precipitins by injecting rabbits with chicken blood, and with milk. Uhlenhuth^{19, 20} and Nuttall²¹ have shed a great deal of light upon the reaction, especially in connection with its specificity, and with its application in forensic medicine. The latter aspect we shall discuss later.

The antigen in the precipitin reaction is, as above stated, a soluble protein and is called "precipitinogen." Satisfactory bacterial precipitinogens may be made by extracting cultures by almost any method. Indeed it has been found that the injection of the whole bacterial cell, either dead or alive, will lead to the formation of precipitins. This is due to the presence of the bacterial protein, which apparently gives rise to both agglutinins and precipitins. If an antigen of whole bacterial bodies is brought into contact with the resulting anti-serum, agglutination will

take place, whereas with the same anti-serum the precipitin reaction will occur if the antigen used in the test proper is made up of the soluble proteins (bacterial extract) of the microorganism concerned.

Certain observers have claimed the production of precipitins by using non-protein antigens, such as ricin and egg albumen digested by trypsin. After a review of the evidence on both sides, Kraus²² decided that there was not yet sufficient data to prove that precipitins could be induced by the injection of non-protein antigens. Zinsser,²³ working in Friedemann's laboratory in Berlin on this problem, using non-protein antigens from horse serum by bacterial putrefaction, obtained negative results, and after a critical review of the experiments of Nicolle, Pick, Landsteiner, Myers and others, he comes to conclusions similar to those of Kraus.

The precipitinogen molecule possesses two groups—a combining group with which it unites with the precipitin, and a zymophore group, which together with the zymophore group of the precipitin molecule has a coagulating or precipitating function. The combining or haptophore group is relatively thermostable, and thus retains its ability to combine with precipitin, even after the precipitating function is lost.

As to the precipitins, little is known of their chemical nature. They are precipitated along with the englobulin fraction of the serum, by ammonium sulphate, and are destroyed by protein-altering substances such as acids and alkalis, pepsin, and trypsin. They develop in the injected animal more slowly than agglutinins, and are more easily destroyed by heat than the latter. Upon heating precipitins to from 50° to 60° C. its ability to cause precipitation in the presence of its specific antigen is lost,²⁴ although it still retains its ability to unite with the latter. This experiment demonstrates its similarity to agglutinins in that it is composed of two groups, a combining or haptophore, and a zymophore group, the latter of which is thermolabile. The presence of the two groups places this antibody in Ehrlich's class of receptors of the second order. Precipitin which has lost its zymophore, or precipitating group is called "precipitoid." If such precipitoid is added to precipitinogen it possesses the power to bind the latter, even in the presence of precipitin. This is accounted for by its greater affinity for the antigen.

While precipitins are specific, they nevertheless exhibit to some degree the "group reaction" spoken of in the section on agglutinins. Just as a typhoid-immune serum will agglutinate to some degree, the bacilli belonging to the typhoid group, viz., the colon bacilli, paratyphoid bacilli, etc., so precipitins against the protein of a certain species will precipitate to some degree the proteins of other animals or bacteria which are closely related. This group reaction is shown by Nuttall by the following table:

ANTIHUMAN PRECIPITATING SERUM		Precipitate
Tested against:		100 per cent
34 specimens human blood	100	" "
8 Simiidae, 3 species	92	" "
36 Cercopithecidae	78	" "
13 Cebidae	50	" "
4 Hapalidae	0	" "
2 Lemuridae		

Thus it is seen that the farther the animal is removed from that for which the serum is specific, the less strong is the reaction. In practical application it is found, as in the agglutination test, that if the immune serum is used in high dilution, all danger of non-specific results is obviated. It is not difficult to produce precipitating serum which will act in a dilution as high as 1:5000. Some antisera have been reported as having a titer 1:100,000 (Uhlenhuth).

PRACTICAL USES OF THE PRECIPITIN TEST.—Space is not available here to describe all the practical applications of the precipitin reaction. It is used in many laboratories for tests such as the differentiation of species or strains of bacteria, in much the same manner as is done by agglutination. Thus we have the precipitin test with sputum, urine or cultures of pneumococci to determine the various types. Precipitin tests are made by health authorities upon various meat products to determine the possibility of adulteration with dog, horse and other foreign flesh in meat mixtures such as sausage, etc. The test has also been used in detecting the presence of cancer, although it has not been found to be sufficiently reliable to warrant its general use for this purpose.

For the technic of these tests the reader is referred to Kolmer's "Infection, Immunity and Specific Therapy."

It is in the practical application of the precipitin reaction to forensic medicine, however, that this phenomenon has proved of greatest value. Thus it is often of importance for the attorneys in a murder case to know whether a given blood stain on garment, floor, or weapon is really *human* blood. In other cases, as in rape, it is important to differentiate between seminal stains and those due to leukorrhea, etc. The technic for such determination is as follows:

The first step is to scrape off a little of the stain and to examine it microscopically, to determine whether blood-cells, spermatozoa, or other formations are present. In the case of a stain suspected of being human blood, even if the corpuscles are not seen with the microscope, a portion of the scrapings should be ground up with a few crystals of sodium chlorid and placed under a cover glass on a slide. A few drops of glacial acetic acid are then allowed to run under the cover-slip and the whole is heated to just about the boiling point for a minute, the acid being replenished when necessary. Crystals of hemin form on cooling and may be seen under the microscope as brown rhombic crystals. A portion of the stain may be dissolved in distilled water, filtered and acidified with dilute acetic acid, and examined spectroscopically.

Having established that the stain is really blood, the next step is to determine its source by the precipitin test.

A highly potent antihuman serum must be prepared. A healthy rabbit is selected and injected, intravenously, with from 2 to 5 c.c. of human serum, in gradually increasing amounts, for three injections at five-day intervals. Nine days after the last inoculation, the serum of the rabbit should be tested against the antigen (human serum) to determine its titer. The results should show a positive reaction with a dilution of the antigen of at least 1:1000. The injections sometimes prove fatal to the

rabbit and for that reason, as well as the fact that some animals do not respond readily with a good immune serum, it is wise to start several animals in order to be sure of at least one. The antiserum should be tested against other proteins such as a dog serum, beef serum, etc., so as to be sure of its specificity.

The stain should be soaked for from 12 to 24 hours in physiological salt solution to extract the blood. It must then be filtered so that the resulting liquid is perfectly clear. The dilution of the blood in such a specimen is always uncertain, but it is sufficiently accurate for practical purposes to determine this by shaking and observing the resulting foam. Protein solutions will show foam on shaking in dilutions as high as 1:1000, and such a dilution is satisfactory for the test. The solution should give a neutral reaction.

The actual test may be performed as follows:

- Tube 1. Unknown solution 1 c.c. + antiserum 0.2 c.c.
- Tube 2. (Control) Known human serum (1-1000) 1 c.c. + antiserum 0.2 c.c.
- Tube 3. (Control) Unknown solution 1 c.c. + normal rabbit serum 0.2 c.c.
- Tube 4. (Control) Saline solution 1 c.c. + antiserum 0.2 c.c.
- Tube 5. (Control) Unknown solution 1 c.c. + Saline solution 0.2 c.c.
- Tube 6. (Control) Extract of unstained clothing 1 c.c. + antiserum 0.2 c.c.

Fresh pipets should be used in handling the various solutions. The immune serum should be placed in the tubes first, and the solution to be tested is allowed to flow slowly down the side of the tube and over the surface of the antiserum, as in Heller's "ring test" for albumin. At the line of contact a fine white ring will rapidly appear. Within five minutes it should be quite definite. Final readings should be taken at the end of one hour, after which the tubes may be shaken, and set away in the ice chest over night. In the morning the amount of precipitate in the various tubes should be noted.

In the above test, the first tube may or may not show a precipitate, depending upon whether or not the unknown solution is human serum. The second tube must always show a positive result, but all the other tubes must be negative. If all the controls are satisfactory and there is a definite precipitate in the first tube, the presence of human blood in the suspected stain is established.

The principle of the precipitin test has been applied to the problem of the determination of pneumococcus types by Blake,²² who elaborated a procedure for this purpose which is dependent upon the presence in broth cultures of pneumococcus of a soluble substance which gives a specific reaction with homologous antipneumococcus serum. The method is as follows:

The emulsion of pneumococci is obtained from the sputum by the mouse method described in the agglutination test. After centrifuging at high speed, the supernatant fluid is water-clear, and is carefully pipetted

off without disturbing the sediment. Four small test-tubes are then set up in a rack and the supernatant peritoneal washings are mixed with equal amounts of antipneumococcic serum as follows:

Tube 1, 0.5 c.c. serum Type I (1:10) + 0.5 supernatant peritoneal washings.

Tube 2, 0.5 c.c. serum Type II (undiluted) + 0.5 supernatant peritoneal washings.

Tube 3, 0.5 c.c. serum Type II (1:10) + 0.5 supernatant peritoneal washings.

Tube 4, 0.5 c.c. serum Type III (1:5) + 0.5 supernatant peritoneal washings.

The reaction is almost immediate in the tube containing the homologous immune serum, while the other tubes remain clear. Atypical Type II pneumococci give a precipitin reaction only with undiluted Type II serum. The presence of other organisms, together with pneumococcus in the peritoneal exudate, does not interfere with the reaction, and herein lies the value of this test, inasmuch as it is available where an impure emulsion would not be suitable for the agglutination test.

A certain percentage of patients suffering from lobar pneumonia excrete in their urine at some stage of the disease a soluble substance of pneumococcus origin, and therefore precipitable. It is present, according to workers at the Rockefeller Institute, in about 65 per cent. of cases due to Types I, II, and III. The technic for performing the test is simple. The urine is centrifuged and 0.5 c.c. supernatant fluid is mixed with an equal amount of antipneumococcic serum Type I. Similar tubes are set up with Types II and III. The precipitate is not usually so definite and clear cut as in the reaction using peritoneal washings. It may appear almost immediately, but it is well as a routine measure to incubate in a water bath at 37° C. for one hour. This test, of course, has little significance when negative, but positive results are quite reliable.

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PHAGOCYTOSIS AND THE OPSONIC INDEX

Phagocytosis.—Elsewhere we have mentioned the rôle played by the leukocytes in accomplishing the destruction of bacteria and other foreign matter in the tissues of the animal body. These cells were observed by Metchnikoff to have a very important bearing on the recovery of the daphnia infected with yeast spores. If phagocytosis occurred freely, the progress of the infection was favorable.

The leukocytes reach the site of an infection as a result of the attraction exerted by chemical substances liberated by the bacteria at this point. This phenomenon is known as *positive chemotaxis*. The chemical stimuli thus produced are sometimes of such a nature that instead of attracting the leukocytes they repel them. This is known as *negative chemotaxis*. Leber¹ was the first to show this chemotactic influence experimentally. He isolated a crystalline substance, which he termed "phagosin," from the bodies of dead cultures of staphylococci. This substance definitely attracted leukocytes to the tissues where it was introduced. More recent studies have tended to show that the attraction or repulsion of leukocytes is due to alterations in the surface-tension of these cells. If the surface-tension is decreased, the cell goes forward, if it is increased, the cell recedes.

By this method of reasoning, it is held that in the case of a local infection the poisons liberated by the bacteria possess the chemical substances necessary for the production of a positive or negative chemotaxis. These chemical substances diffuse toward the surrounding capillaries, and reach the side of the leukocyte toward the infected area first. The surface-tension of this side is thus lowered, and the leukocyte immediately proceeds in that direction. Since the chemical substances will be found in greatest concentration at the stomata or the capillary wall through which they reach the blood stream, the leukocytes are thus attracted to these stomata, and work their way through to the surrounding tissues. Once outside the vessel wall the same influences are exerted to draw them toward the actual infected area, and thus the leukocytes form a wall around the bacteria.

It is suggested, according to this theory, that those cells possessing

the most mobile cytoplasm will be affected most. This would explain the preponderance of polymorphonuclear leukocytes over the lymphocytes at such an infected area.

The chemical nature of chemotactic substances is a matter for conjecture. In infectious processes it is believed that the bacterial poisons, such as true toxins and endotoxins, as well as the bacterial protein of dead microorganisms are the substances mainly responsible for the occurrence of both positive and negative chemotaxis. It is well known that the more virulent a bacterium becomes, the less likely are the leukocytes to ingest it. Just what this is due to is not known. It may be true that virulent bacteria are able to excrete a substance antagonistic to phagocytes (virulins of Rosenow, aggressins of Bail). This is in accordance with the theory propounded by Welch in 1902, referred to in the section on Virulence. However, it is not yet settled as to whether there is in reality such a thing as *negative* chemotaxis. In cases of infection in which there is a leukopenia either local or general, it may be that the very substances which attract the leukocytes are powerful enough to paralyze by overstimulation, or to destroy them in large numbers by their toxic action. Metchnikoff asserted that leukocytes might, after a time, be attracted toward substances that would kill them. As the infection proceeds favorably, it is therefore conceivable that, with the diminution in numbers or attenuation in virulence of the bacteria responsible for the disturbance, the leukocytes attracted to the area will again be able to survive, and gain the ascendancy. This may occur in cases such as pneumonia, or appendicitis, where an apparent primary negative chemotactic phase is succeeded by a leukocytosis.

The fate of the ingested bacteria probably varies according to the variety and virulence of the microorganism. It has been shown that the leukocyte possesses a lytic enzyme in its cytoplasm whose function is to digest all manner of phagocytized particles. This *endolysin* is non-specific, and is rather resistant to heat. That many of the engulfed bacteria are not destroyed, however, is amply shown by various experiments. Cultures may be obtained from gonorrheal pus in which film preparations fail to demonstrate any extracellular gonococci. It is suggested by some² that infection may be carried from one area of the body to another by leukocytes which have engulfed living virulent bacteria.

Opsonins.—Although Metchnikoff's researches on the importance of phagocytosis in the production of immunity have had a far-reaching influence upon our conception of the phenomena involved, his conclusions have not been allowed to go unchallenged. Wright, Neufeld, and their collaborators have shown that even in those infections where phagocytosis seemed to play a most important part in the protection of the individual, the leukocytes, when separated from the serum, have little or no phagocytic power. They further showed that the serum of normal individuals, but especially those who have recovered from infection, possesses the power to increase the phagocytosis, when brought into contact with the leukocytes and with an emulsion of bacteria. This peculiar power of the serum was demonstrated to be due to substances in solution

called *opsonins* (Wright), or bacteriotropins (Neufeld), which act not upon the leukocyte, but upon the bacteria, preparing them, as it were, for ingestion. This action is clearly illustrated by the following experiment:

1. Washed leukocytes + immune serum + bacterial emulsion == phagocytosis.
2. Washed leukocytes + saline solution + bacterial emulsion == no phagocytosis.
3. Washed leukocytes + immune serum incubated for 1 hour at 37° C., then leukocytes washed in saline and bacterial emulsion added : no phagocytosis.
4. Immune serum + bacterial emulsion incubated for 1 hour at 37° C., then bacteria washed in saline and leukocytes added == phagocytosis.

The opsonins of the immune serum are thus proved to have no direct relation to the leukocytes, but seem to produce a change in the bacteria, which renders them more liable to phagocytosis—in other words, more appetizing to the leukocytes. This important discovery threw new light upon the relation of phagocytosis to immunity, and necessitated a reconstruction of Metchnikoff's theory. It is evident that in future the true conception of the defensive mechanism of the body must include both the cellular and the humoral theories, both of which are important, and in many ways interacting.

Normal serum possesses opsonins, although their concentration or potency falls far below those found in immune serum. The question of the specificity of normal opsonins has been the subject of much investigation. Muir and Martin³ have brought out the great similarity of these substances to the complement, or alexin. Both are thermolabile, being destroyed by exposure to 56° C. for half an hour. They have further shown that if a normal serum is brought into contact with an antigen and its specific antibody, the resulting reaction which absorbs the complement also absorbs the opsonin. They therefore concluded that normal opsonin, like the complement, is non-specific.

This view is challenged by various workers, as Neufeld⁴ and Dean,⁵ who believe that the parallelism between complement and normal opsonin is evidence to show that opsonin requires the complement to activate it, just as we shall see later is required by a lytic sensitizer. It has further been shown that procedures which remove the complement from a normal serum do not remove *all* the opsonic power. From this we may infer that normal opsonin is a feeble but specific antibody, requiring for its activation fresh complement or alexin.

It has been shown by Bulloch and Western,⁶ Rosenow⁷ and Hekloen,⁸ that emulsions of a given organism will absorb from normal serum their specific opsonin, leaving the opsonin for other bacteria apparently intact. This work would lead us to believe that normal opsonins are specific, but depend for their action upon a thermostable substance and

a thermolabile substance which resembles the complement, and which, indeed, it may be identical. The experiments of Cowie and Chapin⁹ have demonstrated that heated normal serum in which the opsonic action had been destroyed could be restored to practically its original opsonic power by the addition of a small amount of the complement—in itself but slightly opsonic.

In the case of immune opsonins, or bacteriotropins, i.e., the opsonins found in the serum of an immunized animal, the action of heat is not apparent. In other words, immune opsonins are thermostabile. Since they are therefore capable of acting after being heated, it is evident that they do not require the presence of complement to activate them. In this connection, however, it is interesting to note that Dean has found that although heated, immune serum is powerfully opsonic, it is rendered still more so by the addition of a small amount of normal unheated serum, in much the same manner as was shown by Cowie and Chapin for normal opsonins. They are strictly specific, and may be absorbed from immune serum by their respective bacteria, in the same manner as that described by Bulloch and Western in the case of normal serum.

We have previously stated that not all bacteria are equally amenable to phagocytosis. As a general rule, virulent, recently isolated microorganisms are more able to resist the influence of opsonins than those which have to a large extent lost their virulence. This resistance is held by some to be due to the capsule which many virulent strains possess, by others to the production of aggressins or virulins by the bacteria, in the process of self-immunization.

The exact rôle which normal and immune opsonins play in immunity is not yet determined. It is generally conceded, however, that their action upon invading bacteria in rendering them susceptible to phagocytosis is an important factor in both natural and acquired immunity. This power of the opsonins is exerted more effectively in some types of infection, as in pyogenic infections, than in others where the immunity is mainly of another variety as in antitoxic immunity. Phagocytes are capable of ingesting enormous numbers of bacteria, and if their action is stimulated by the presence of both normal and immune opsonins, they are bound very materially to influence the course of infection.

The Opsonic Index.—Based on the discovery of immune opsonins, or bacteriotropins, in the serum of patients suffering from infections of various sorts, and in that of individuals who have recovered from such infections, Wright and Douglas, Neufeld and Rimpau, and Leishman have devised a technic with certain modifications according to the workers, which enables the observer to watch the effect of various methods of specific therapy, especially of vaccination with bacterial vaccines, by estimating the immunity as indicated by the opsonic power of the serum.

The method is based on the comparison of the opsonic power of the patient's serum with that of serum from a normal individual of the same species. The result of such a comparison is recorded as the opsonic

index. This may be defined as the ratio of the number of bacteria ingested per leukocyte in the presence of the patient's serum, to the number ingested per leukocyte in the presence of normal serum.

Wright and his collaborators desired in this way to inform themselves regarding the condition of the patient from an immunologic standpoint. They felt that if this could be done from time to time during the course of administration of bacterial vaccines, they might have some reliable guide as to optimum size and interval of dosage, and an indication as to when an immunity is established. A vast amount of work has been done with this end in view, and while the results have not by any means fulfilled the expectations of immunologists, they have been instrumental in adding very materially to our knowledge of some of the processes underlying vaccine therapy.

The reasons for the failure of the method as a practical guide in following the immunity response to infections and vaccines may be summarized as follows:

1. The technic is most laborious and time-consuming, rendering the method impracticable in regular practice.

2. The technical difficulties involved in performing the test necessitate the employment of highly-trained laboratory workers, making the procedure too expensive, in view of the limited value of the results obtained

3. The chances for error, even in the hands of the most expert technicians, are very considerable, and results obtained by competent workers using the same serum may show variations. It must be said, however, that with strict attention to details, the worker will usually obtain valuable information. This fact renders the procedure of sufficient value to warrant its use in laboratory or scientific clinical investigations.

4. The test assumes that the leukocytes are a constant factor, whereas it has been shown that during infection the leukocytes undergo qualitative changes *in vivo*, while the leukocytes used in the test *in vitro* are normal, and therefore may be a source of error.

In this connection it may be well to mention the work of Park and Biggs,¹⁰ and of Glynn and Cox,¹¹ who have shown that the phagocytic powers of various emulsions of leukocytes differ widely. It is found that it is also important to use emulsions containing approximately the same number of leukocytes, for, if unequal emulsions are used, those having the greatest number of cells show less phagocytosis per cell than the less concentrated preparations. Ruth Tunncliffe¹² has shown that at birth the leukocytes are less active than in adult life.

In spite of these inherent sources of error, and the limitations in its use as a routine measure, the test has a definite value in the investigations of many immunological problems with which the research worker is confronted. A brief description of the technic is therefore not out of place.

Four constituents are necessary for making the test:

1. Patient's serum.
2. Normal serum for control.
3. Bacterial emulsion.
4. Leukocytic emulsion.

The serum of the patient and that from a normal individual may be obtained by the methods described in the section devoted to agglutinins. It is well to pool the sera of several normal persons for the controls.

The bacterial suspension must be uniform, free from clumps, and must not be agglutinated by the control serum, or by the patient's serum. Cultures should be grown on agar slants for from eighteen to twenty-four hours, scraped off into sterile physiologic saline solution, and thoroughly shaken to break up the clumps. Centrifuging at low speed may be necessary to remove gross particles. As a rule, the suspension should contain approximately 500,000,000 bacteria per cubic centimeter, although experience will be necessary to determine the optimum density.

The leukocytes are usually obtained by pricking the finger of a healthy person, and allowing fifteen drops of blood to run into a test-tube containing 4 c.c. of sterile 2 per cent. sodium citrate solution in normal saline. This should be thoroughly mixed, and centrifuged at high speed. This throws the red cells to the bottom, and leaves a light, buffy coat of leukocytes on top. These are gently taken off with a pipet, and constitute the "leukocytic cream" of Wright's experiments.

Equal quantities of unknown serum, bacterial emulsion and leukocytic suspension are mixed thoroughly in a capillary pipet. The tip is then sealed in the flame, and the mixture incubated for from fifteen to thirty minutes at 37° C. The pooled normal serum is treated in an exactly identical manner. At the end of the incubation time, smears are made upon slides, and these are stained as described in the technic for standardizing vaccines by Wright's method (page 232 *et seq.*). The number of bacteria ingested in one hundred or more leukocytes is then counted in each preparation. Suppose the total count in the case of normal serum is 650 bacteria per 100 leukocytes—a *phagocytic index* of 6.5 per leukocyte; in that of unknown serum 1300 per 100 leukocytes or 13 per leukocyte. In this example, the opsonic index, according to our definition, would be $\frac{13}{6.5} = 2$, a high value.

The technic of Neufeld possesses certain advantages over that of Wright. It consists in making a number of dilutions of both normal and unknown serum, and determining the highest dilution in each that still shows phagocytosis. No note is taken of the number of bacteria ingested, but the quantitative estimation of the opsonin present is based on the demonstration of the *point of opsonic extinction*. It also differs from the technic of Wright in that the serum is deprived of its complement (themolabile opsonin?) before the test is made.

The test is performed as follows:

1. The serum, that to be tested, as well as the normal serum, is

heated to 55° C. for one-half hour to destroy the complement. Old serum need not be so treated, as the complement gradually deteriorates on standing. A parallel series of dilutions with physiologic saline solution is made in a series of small test-tubes. The following dilutions are suitable: 1:10, 1:20, 1:50, 1:100, 1:200, 1:400, 1:600, 1:800, etc.

2. Mix 0.1 c.c. of each dilution of immune serum with 0.1 c.c. of bacterial emulsion. Plug each tube with cotton. Incubate for one hour.

3. Add 0.1 c.c. leukocytic emulsion to each tube. If the emulsion is weak, it may be necessary to add more than this quantity. Mix and incubate for 15 minutes to two hours, according to the variety of micro-organism. Such bacteria as the typhoid bacillus and the cholera spirillum are digested very rapidly after ingestion by the leukocytes, and after ten or fifteen minutes are partly disintegrated, will stain indistinctly, and cannot be determined with accuracy.

4. After the second incubation the leukocytes will have settled to the bottom. The supernatant fluid is carefully pipetted off, and films of the leukocytes made on glass slides and stained.

5. A large number of fields in each slide are examined under the microscope, and the weakest dilution which still favors phagocytosis is noted. This dilution is called the *point of bacteriotropic (or opsonic) extinction*, and should be determined for both the immune and the pooled normal serum. No attempt is made to count the phagocytosed bacteria.

Practical Value of the Opsonic Index.—By the careful use of his method, Wright and his collaborators have furnished some very interesting observations. In a series of cases of chronic staphylococcus infections, they showed that the opsonic index is uniformly low, and they conclude that under such depressed phagocytic powers, the staphylococci gain headway, whereas in a normal individual the same bacteria are unable to obtain a foothold, since they would fall prey to the leukocytes soon after entering the body.

They found, further, that during treatment of such patients with vaccines composed of dead staphylococci, the opsonic index consistently rose, and that with this rise there was a striking improvement in the clinical picture of the patient. Immediately after the inoculation, however, they found a temporary depression of the opsonic power, lasting about twenty-four hours. This is called the *negative phase*, and is immediately succeeded by a rise above that which preceded it.

Wright thought that the most important function of the estimation of the opsonic index was that of guidance as to the size and frequency of doses of bacterial vaccines in the treatment of disease. This expectation has not been realized, owing chiefly to the laborious nature of the procedure, which renders it impracticable save for laboratory investigations in the field of research.

The test has been of considerable practical importance, however, in demonstrating the occurrence of the condition known as the negative phase. A similar phenomenon is found in all processes of active immunization. Salomonsen and Madsen¹³ obtained a curve illustrating such temporary fall in antibody content immediately following the in-

oculation of a horse with diphtheria toxin. Brieger and Ehrlich¹⁴ have demonstrated an analogous condition in a goat treated with tetanus toxin, and Jorgensen and Madsen¹⁵ in studies upon agglutinins.

It is obviously a dangerous thing to administer a large dose of vaccine to a patient still in the negative phase following the preceding inoculation. Such a practice has been shown to lead to a "summation of the negative phase" which may last for several months. In this way the injudicious use of vaccines may be productive of great harm, and physicians should be warned against the too rapid repetition of inoculations. Since the routine use of the opsonic index test, or the estimation of the bacteriotropic titer, is precluded for reasons given above, the most reliable guide is to be found in a consideration of the *reaction* of the patient. The *local* reaction should consist in an area of redness and slight swelling about the point of inoculation. It should not be sufficiently extensive to cause marked discomfort, although in cases where immunization is to be carried out in one, two or three inoculations, as in antityphoid vaccination, the dosage is necessarily large, and may cause extensive local reaction. The *focal* reaction consists in signs of activity about any lesion for the treatment of which the vaccine is being used. Slight hyperemia is probably of advantage in bathing the parts with the bactericidal substances of the serum, but excessive focal reaction must be avoided, for fear of aggravating the condition by causing irritation with a lowering of the resistance of the tissues. A *general* reaction is evidenced by a feeling of malaise, often with a rise in temperature, and headache. In anti-typhoid vaccination this is not uncommon, but as a rule such a reaction is to be avoided, since during such a phase the patient is obviously below par, and is liable to intercurrent infections, or to a flare-up of the disease for which he is being treated.

According to Wright, a patient may be therapeutically inoculated from his own lesions by such measures as will increase the local circulation, thereby absorbing more of the specific antigen into the general blood stream. Such a method is termed "auto-inoculation" and must not be confused with "autogenous" vaccination, in which the organisms are isolated from the patient's own lesions and made into a vaccine for subsequent injection. An illustration of the use of auto-inoculation is given by Wright in a case of gonorrheal arthritis in which the joints were massaged, with results upon the opsonic index in every way analogous to those produced by the injection of bacterial emulsions. The main objection to this method lies in the impossibility of accurately estimating the dosage, and its use is therefore not to be recommended, excepting, perhaps, in the case of such infections as that of the prostate, where gentle massage is of value, not only as an auto-inoculation, but also as a means of securing drainage for pent-up pus.

In active pulmonary tuberculosis, and in other subacute infections accompanied by a rise in temperature and by other systemic signs or symptoms, it is likely that the body is already trying to cope with excessive amounts of antigen, and vaccine treatment of any kind is not only superfluous, but actually dangerous. The same line of argument

is even more applicable in cases of acute infections such as typhoid fever, pneumonia, etc., in which a certain element of the profession, influenced by the extravagant claims of commercial manufacturers and distributors of vaccines, and encouraged by overenthusiastic therapeutists, are making indiscriminate use of all sorts of vaccines, in the hope of favorably influencing the course of the disease.

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HEMOLYSINS, BACTERIOLYSINS, AND OTHER CYTOTOXIC SUBSTANCES

Phenomena of Lysis.—We now come to a consideration of those antibodies which, according to the theory of Ehrlich, belong to the third order. These immune substances require for their action the presence not only of antigen, but also a third constituent of the blood called complement or alexin. For this reason Ehrlich argued that these receptors of the third order must possess not only a haptophore group which unites with the antigen, but also a haptophore group which unites with the complement.

Because of the double construction of this receptor, it is called an *amboceptor*, and is apparently the link between antigen and complement. These amboceptors are remarkably specific for their respective antigens. The latter are usually cellular in type so far as is known, and these cells undergo lysis as a result of the action of the amboceptor and complement.

The first important step in regard to lysins after the discovery of alexin by Buchner was made by Pfeiffer, who found that the injection of cholera spirilla into the peritoneal cavity of a guinea pig which had previously been immunized against cholera resulted in the solution

of the spirilla. This is now called the "Pfeiffer phenomenon." If small quantities of the peritoneal exudate were removed with a capillary pipet a few minutes after the injection, and examined under the microscope, it was observed that the spirilla had become granular, swollen, and were losing their staining properties. These changes became more marked as time went on, until in an hour or so all signs of the microorganisms had disappeared. The animal subsequently showed no signs of infection. He further discovered that this action was specific, for when he injected other bacteria into a cholera-immune guinea pig, no such dissolution occurred, and no such protection against infection was apparent. The serum of such a cholera-immune guinea pig, transferred to the peritoneal cavity of a normal animal, was found

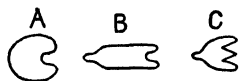


FIG. 5.—EHRlich's SIDE-CHAIN THEORY, SHOWING COMPOSITION OF THE SIDE-CHAIN OF THE THIRD ORDER.

- A, Antigen.
B, Amboceptor or sensitizer.
C, Complement or alexin.

to protect the latter against a fatal intraperitoneal injection of cholera spirilla. This was true even where the serum had been heated to 56° C. for one-half hour.

Here, then, it was apparent that the animal had been protected against infection by the action of lytic substances in the serum of an immune animal, whereas it was found that serum from a normal animal possessed no such protective power. This action of the immune serum was specific, and the protection could be transferred from one animal to another by the injection of immune serum together with the bacterial emulsion. In an animal passively immunized in this way, the lytic action upon the bacteria is observed in an exactly similar manner to that taking place in the actively immune animal. Moreover, the fact was established that the immune substance is thermostabile.

Pfeiffer thought that the bacteriolysis occurred only within the animal body, and could not be accomplished *in vitro*. For this reason, although he appreciated the importance of the phenomenon as an argument in favor of the humoral theory of immunity, he assumed that the cellular elements were necessary to carry out the reaction. Metchnikoff¹ succeeded in obtaining extracellular lysis by adding to the mixture of cholera spirilla and heated immune serum, small quantities of leukocytic extract. He thus claimed to show the relationship of Pfeiffer's phenomenon to the rôle of leukocytes in immunity.

Bordet² a little later showed that what was really requisite for the carrying out of the test was a little fresh normal serum. He found: (a) Fresh immune serum was very active: (b) Heated immune serum was inactive: (c) Fresh normal serum alone had no effect: (d) Heated immune serum plus fresh normal serum had powerful effects. In other

words, what was needed besides the thermostabile immune substance, was some thermolabile substance present in all fresh serum, normal or immune. This latter serum element, no matter from what source it was derived, produced the same result, and had no influence upon the specificity of the reaction. This substance corresponds to Buchner's alexin.

Further experiments by Bordet upon guinea pigs using rabbits' red blood corpuscles as antigen enabled him to show that these lytic immune substances, while specific in their production and action, were not limited to bacterial cells, but could be obtained in response to such antigens as red blood-cells. This lytic immune substance (hemolysin) obeyed laws similar to those observed in the case of bacteriolysins, i.e., it was rendered inactive by heating to 56° C. for one-half hour, was reactivated by adding fresh normal serum (alexin or complement), was specific, and this specificity was again demonstrated to be due to the immune substance (hemolysin), and not to the alexin or complement.

At this stage, Ehrlich began experiments designed to discover the relationship of these phenomena to his side-chain theory. Working with Morgenroth,³ he attempted to show that these side-chains or receptors (hemolysins, bacteriolysins), made up of two haptophore groups, one for uniting with the cell (antigen) and the other with the complement, would unite with the antigen, and thus be absorbed out of the immune serum. They placed in a test-tube washed beef corpuscles along with inactivated serum from a goat immunized against beef cells. After incubation for one hour at 37.5° C. they centrifuged the mixture and placed the supernatant fluid and corpuscle sediment in separate tubes. To the former they added washed beef corpuscles and fresh normal goat serum (complement). There was no change. To the latter they added normal goat serum (complement) and saline to make up the volume. Hemolysis occurred.

Thus they showed that antigen will absorb from immune serum its specific antibody in much the same way as Bulloch and Western absorbed the specific opsonin from serum, by treating it with emulsions of bacteria. They also show that the amboceptor, or antibody, unites with the antigen in the absence of complement, but hemolysis does not take place until the latter is supplied. This is an exceedingly important observation which was later confirmed by Bordet, who spoke of such a union of antigen with amboceptor in the absence of alexin or complement, as a "sensitization" of the antigen, and he named the amboceptor *sensitizer* or "substance sensibilitrice."

That amboceptor or sensitizer unites in this way directly with the antigen with such firm union even at temperatures as low as 0° C. illustrates how great is the affinity of these substances for each other. When thus united, the sensitized cells—whether bacterial cells or red corpuscles—may be washed thoroughly in an effort to separate the sensitizer from them, but subsequent addition of complement to the washed cells, with resulting lysis, indicates the firmness of their union.

A similar experiment was made to determine the method of action of the heat-sensitive substance (complement or alexin). To an emulsion

though for practical purposes it lends itself very readily to the search for a simple and satisfactory explanation of the phenomena with which we are dealing. There does not appear to be any direct and positive experimental evidence to permit one to decide between Ehrlich's and Bordet's views.

Bordet's discovery of hemolysins stimulated a tremendous amount of research into the nature of lysins, and since hemolysins can be studied with great ease and accuracy, on account of the readiness with which the reaction may be measured by the amount of hemolysis occurring, the nature of the phenomena associated with lytic sera was worked out mostly by the use of hemolysins. These studies aided greatly in a correct understanding of the mechanism of bacteriolysis, for it was found that the same underlying principles were applicable to all lytic reactions, namely, the necessity of having the following three factors in carrying out such reactions: antigen (blood, bacterial or other cells), antibody (thermostabile), and complement (thermolabile).

The Nature of Complement.—Complement is the substance, present in all fresh sera, which acts with an amboceptor to produce lysis. It is thermolabile, being destroyed by heating to 56° C. for a few minutes. It is identical with Bordet's alexin. Following the work of Nuttall, Buchner showed that the active principle causing bacteriolysis weakens on standing, is destroyed by heat, dialysis, or by dilution with distilled water. To this active principle he gave the name "alexin." At this time nothing was known of the part played by amboceptors in such lytic processes, and Buchner believed that alexin was comparable to a proteolytic enzyme. It was not until 1899 that Bordet found that the alexin of Buchner was composed of two distinct substances—one, with sensitizing properties, is thermostabile, the other, the activating substance, is thermolabile. The latter he called alexin. Shortly after, his observations were confirmed by Ehrlich and Morgenroth, but instead of using the term alexin, Ehrlich chose the word complement (that which completes).

It will be remembered from our discussion in another section, that there is no proof as yet brought forward to show whether complement is present in a free state in the circulating plasma, or whether it exists as such in the tissue cells and leukocytes, and is liberated into the serum during the process of clotting of the blood. Buchner suggested that it might be a secretory product of the leukocytes, and Metchnikoff strongly supported this view as to the origin of "cytase," which corresponds to Buchner's alexin. Neufeld⁷ treated red cells with hemolysin, and after being thus sensitized they were allowed to be ingested by washed leukocytes. He found that they were not hemolyzed, but were broken up in an entirely different manner. This he took to prove that alexin or complement is not present inside the leukocytes. Zinsser examined for the presence of complement emulsions of leukocytes which had been kept at 37° C. for several days, but his results were negative. He points out, however, that there was no way of knowing how long the leukocytes lived, and he therefore felt that the experiment was incon-

elusive. The absence of complement in the aqueous humor of the anterior chamber of the eye, and in the cerebrospinal fluid, has been held by some to be due to the absence of leukocytes in these fluids. Gengou⁸ bled animals through a paraffined cannula directly into paraffined tubes, thus avoiding all cell injury and consequent clotting of the blood. The plasma from such blood, he claimed, possessed no bactericidal properties, and these results were held to prove that circulating blood-plasma contains no complement. Gengou's findings have not been universally confirmed, and although a large amount of work has been done upon this subject, the problem has not yet been solved.

Nearly all workers who have occasion to prepare guinea pig serum for use as complement have noted that such serum, if separated from the clot a few minutes after bleeding the pig, may contain very little complement, but that if it is allowed to stand for a few hours its potency is greatly increased. The majority of serologists bleed the guinea pigs the day before they wish to use the serum, so as to allow the complement content to increase to its maximum. This tends to support the view that leukocytic changes are necessary to the liberation of complement, but as pointed out by Zinsser, it may depend rather upon any one of the numerous factors involved in the complicated process of coagulation.

Certain workers have regarded the liver as a source of complement, while others have claimed the same for the thyroid gland, and for the pancreas. In a general way, however, the evidence points to the leukocytes as the chief, although not necessarily the sole, source of supply.

In many respects, complements bear a close resemblance to ferments. The rôle they play in the processes of cytolysis, and their thermolability, point to the analogy between them and ferments. Their disappearance during the process of cytolysis, however, argues against their ferment-like nature, but there is some evidence to show that, like ferments, they are merely rendered inactive by the products of their own action. Liefman and Cohn⁹ claim that the complement is not used up by reason of its union with amboceptor and antigen, but is rather absorbed by the end-products of the reaction, such as the stromata of the red cells, etc. Kiss¹⁰ showed also that the action of complement depends largely upon its concentration, and that the quantitative relationship which was said to exist between the complement and the cells or bacteria upon which it could act was not so strict as had been supposed.

If the functional activity of complement is not fully understood, its chemical nature is still more obscure. Kyes found that certain lipoidal constituents of red cells, as lecithin, have a complement-like action, but Von Dungern and Coca¹¹ showed that this action was due, not to the union of amboceptor and lecithin, but to a splitting of the lecithin into hemolyzing substances, which accounted for the phenomena observed by Kyes. Von Liebermann¹² and Noguchi¹³ showed that soaps isolated from blood-cells and various tissue cells possessed properties closely an-

alogous to those of complement. Sensitized blood-cells are hemolyzed by mixtures of soaps and inactivated guinea pig serum. These serum-soap mixtures, like true complement, are inactivated by heating to 56° C. Other observers, however, as Hecher,¹⁴ and Friedmann and Sachs,¹⁵ were unable to confirm these results and it may be said that while further researches along these lines may materially advance our knowledge of the chemistry of complements, the question is by no means near a satisfactory explanation.

Nor is the question as to the multiplicity of complement satisfactorily settled. Bordet believes that only one complement is present in any given serum, although he agrees with other observers as to the presence of different complements in different sera. That is to say, all agree that a given complement may be strong for a certain hemolytic complex, but weak for a certain bacteriolytic complex, whereas complement from another species may have quite the reverse relation to such combinations. Ehrlich and his followers, on the other hand, claim that a given serum may contain a number of different complements. They claimed to show that complement which passed through Pukall filters, activated sensitized guinea pig cells, while the complement of the same serum, which failed to pass through the filter, was able to activate sensitized rabbit cells. They also showed that by digesting fresh goat serum which was able to activate different hemolytic amboceptors, with papain, the complement for one amboceptor was destroyed, while those remaining were left practically intact. By further treating with soda solution, other complements were destroyed. They also showed that by sensitizing different blood-cells with homologous amboceptors and adding these to a fresh serum for a short time, some complements would be destroyed, while others would be left behind practically unaltered. They claimed as a result of these experiments that complements do not all possess identical haptophores, although the cytophilic groups probably are alike.

While their evidence has not convinced the Bordet school, Ehrlich and his collaborators have succeeded in obtaining considerable support for their views. The problem is of more theoretic than practical interest, since it has been demonstrated that guinea pig serum furnishes satisfactory complements for hemolytic, bacteriolytic and other complexes.

Bordet-Gengou Phenomenon of Complement-fixation.—In the effort to bring experimental evidence to support the view of the functional unity of complement, Bordet¹⁶ cites the results of his work with Gengou in connection with the fixation of alexin or complement by bacterial antigens and their specific sensitizers or amboceptors. They immunized a horse against plague bacilli, and utilized its heated serum as their antibody or amboceptor. For their antigen, they used an emulsion of a 24-hour slant of plague bacilli. Fresh guinea pig serum provided the alexin or complement. Tubes were set up containing the following mixtures:

- Tube 1. **Plague bacilli (antigen) + antiplague serum (antibody) + complement.**
 Tube 2. **Plague bacilli (antigen) + heated normal horse serum + complement.**
 Tube 3. **Antiplague serum (antibody) + complement.**
 Tube 4. **Heated normal horse serum (antibody) + complement.**
 Tube 5. **Plague bacilli (antigen) + antiplague serum.**
 Tube 6. **Plague bacilli (antigen) + heated normal horse serum.**

These tubes were shaken and set aside for five hours. At the end of this time there was added to each tube a quantity of rabbits' corpuscles previously treated (sensitized) with a hemolytic serum. The tubes were then incubated for one hour, and the results noted.

Hemolysis occurred in all the tubes except Nos. 1, 5 and 6. Tube 1 contained antigen, antibody and complement, and it was evident that with the union of the first two elements the complement had been bound, leaving none to activate the sensitized corpuscles which were added later. In tubes 5 and 6, no complement had been supplied at any time, hence the absence of any action upon the sensitized corpuscles. In tubes 2, 3 and 4 no antibody was supplied, so no complement was bound, and it was free to act upon the sensitized corpuscles added later. Similar results were obtained with other bacterial cultures and their antisera.

Bordet argued from these experiments that the same complement that activated sensitized bacteria, causing bacteriolysis, could also activate sensitized corpuscles, causing hemolysis, and regarded this fact as upholding his contention regarding the functional unity of complement.

The phenomenon of Bordet and Gengou was destined, however, to assume much greater practical importance than its authors contemplated. It was soon shown that the principle involved could be utilized to determine whether or not a given serum contained antibodies. A result showing no hemolysis would necessarily imply that an antibody had been present in the tested serum, while hemolysis would indicate its absence. It will thus be seen that the sensitized corpuscles added in the latter stage of the experiment are entirely analogous to the "indicator" used to determine the presence or absence of acid or alkali in a given liquid. Just as phenolphthalein turns red in the presence of acid, so sensitized corpuscles become hemolyzed in the presence of complement. It is upon this presence or absence of free complement after the first incubation that the whole test depends. The fact that the indicator in the test happens to involve another antigen-antibody-complement reaction is merely an accident. If we possessed a simple chemical indicator to detect the presence of free complement, the results of the test would be unaltered.

Not only was it shown that this test could be applied to determine the presence or absence of a specific antibody in a given serum, but it was also demonstrated that, with known immune sera of various kinds at hand, bacterial cultures of unknown identity could be differentiated. This latter use of the test has not become general, however, owing to

the fact that the same information can be obtained by utilizing the Gruber-Widal phenomenon of agglutination as described in the chapter devoted to agglutinins. Bordet and Gengou¹⁷ used the method in establishing the etiological relationship of *B. pertussis* to whooping cough, by demonstrating the presence of the specific antibody for this organism in the serum of children suffering from the disease.

Gengou¹⁸ also showed that the complement-fixation phenomenon was not only applicable to cellular antigen-antibody complexes, but was also of use in cases where the antigen was composed of a soluble protein. It thus appears that the fixation of complement is a generalized property of all complexes involving antigen and antibody, whether the antigen be cellular, as with red blood-cells or bacteria, or a soluble protein as egg-white, animal serum, or alcoholic extract of muscle tissue. This observation of Bordet is of immense importance in relation to the practical applications of the phenomena as devised by Wassermann, Neisser, and Bruch in the diagnosis of syphilis, and of Neisser and Sachs in the determination of proteins for forensic purposes.

Practical Applications of the Complement-fixation Phenomenon:

The Wassermann Reaction.—In 1905 Wassermann and Bruck¹⁹ showed that in performing the experiment of Bordet and Gengou, it was not necessary to use as antigen emulsions of whole bacteria, but that extracts from bacterial bodies could be utilized even more successfully because they were less liable to bind the complement non-specifically. During experiments in connection with complement-fixation in tuberculosis, it occurred to Wassermann and Bruck that the method might be applied to the diagnosis of syphilis. This disease was being extensively investigated by Neisser, as the discovery of *Spirocheta pallida*, just made by Schaudinn, and Hoffman, had drawn the attention of the medical world to syphilis. Together with Neisser, Wassermann and Bruck²⁰ made careful studies upon experimental syphilitic monkeys, and found that positive results could be obtained in an extraordinarily definite and specific manner. While this work was being done, Detre²¹ was applying the same methods to a small number of syphilitic human beings, and published fairly satisfactory results two weeks after the paper of Wassermann and his co-workers appeared. From that time on various observers, working with human syphilitics, published results confirming and extending the original reports, and the procedure rapidly became a routine laboratory procedure throughout the medical world.

The early investigators used as antigen in their tests of syphilitics an aqueous extract of the liver of a congenital syphilitic fetus. As is well known, such an organ contains enormous numbers of spirochetes, and in the absence of successful methods for culturing the microörganism, they felt that this material offered the most promising source of a specific extract of the virus. It was quite natural that in the early conception of the reaction it was assumed to be a simple and direct application of the Bordet-Gengou phenomenon, requiring a specific syphilitic antigen to be united to a specific syphilitic antibody, thus fixing the complement. It was soon found that antigens could be prepared by

extracting normal organs. Marie and Levaditi²² demonstrated that an extract of the liver of a normal fetus was capable of acting as an antigen in the Wassermann reaction. Weygandt²³ showed a similar result by using an extract of normal spleen. Finally, Landsteiner, Müller and Pötl²⁴ found that equally good results could be obtained by using an alcoholic extract of guinea pig heart. Various researches now confirmed the belief that the essential antigenic substances were alcohol-soluble, and thus of the nature of lipoids. Many artificial lipid solutions were tried as antigens, including lecithin by Porges and Meier, sodium taurocholate and glycocholate by Levaditi and Yamanouchi, cholesterin and vaselin by Fleischmann; oleic acid by Sachs and Altman; acetone-insoluble fractions of alcoholic extracts by Noguchi, sodium oleate, lecithin and oleic acid by Sachs and Rondoni. Browning and Cruikshank²⁵ found that the addition of cholesterin to organ extracts greatly enhanced their value, and this observation has been confirmed and utilized by Sachs,²⁶ Walker and Swift,²⁷ McIntosh and Fildes,²⁸ and others.

These findings were a great disappointment to the serologists at that time, since their confirmation involved the abandoning of the idea of specificity in regard to this test. The recognition of this fact, together with the fact that the use of the test by inexperienced and unskillful persons introduced many sources of error, had the effect of temporarily shaking the confidence of the medical profession in the practical value of the reaction. It is only recently that with further study and carefully controlled investigation it has been found that the non-specificity of the antigen has no practical significance in the use of the test. Indeed, it has been shown by Craig²⁹ and others that antigens made of cultures of *Spirocheta pallida*, although specific, are of inferior worth in the practical application of the reaction.

As to the real nature of the Wassermann reaction, it must be admitted that we are very much in the dark at present. Obviously it is not a specific antigen-antibody reaction. Such a specific reaction probably takes place when cultures of *Spirocheta pallida* are used as antigen, and the work of Noguchi,³⁰ and of Craig and Nichols³¹ tend to show that the true syphilis antibodies appear after treatment and are not present in detectable quantities early in the disease. For this reason, as a diagnostic measure, the Wassermann reaction is of much greater value than a true specific complement-fixation reaction. It is obvious that the antibodies concerned in the Wassermann test are not *protective* to the patient. If they were, they would not be likely to accumulate in relatively large amounts early in the disease, when the lesions are at their height, only to disappear after the patient has been successfully treated and all signs of the disease have vanished. It is probable, therefore, that it is not an immunity reaction but is rather an expression of active injury to tissue-cells caused by the spirochetes liberating altered lipoidotropic products, which react with the lipoidal antigen with fixation of complement. This physicochemical theory would tend to explain the findings of Wolfsohn,³² who showed that during anesthesia the Wassermann reaction may become positive. In this case

the narcotic is dissolved in the lipoids in the brain and liberates Wassermann-reaction bodies.

TECHNIC OF WASSERMANN REACTION.—(1) *Collection of Serums to Be Tested.*—Blood may be taken from the vein at the bend of the elbow by using either a syringe or an 18-gauge needle to which is attached a piece of rubber tubing three inches long. The blood is allowed to run into a sterile test tube and left to clot. At least 5 c.c. should be obtained. No trouble will be experienced in obtaining blood if a tourniquet is placed around the arm above the elbow. In young children it may be necessary to withdraw the blood from the external jugular vein. This is easily accomplished by placing the child on its back upon a table and allowing the head to be depressed over the edge, below the level of the body. The veins will become distended, and the procedure is facilitated if the child cries, although this is by no means necessary. Label the tube with a gummed label on which is written the name or number. A book or card index should be kept in which all particulars, including the date, age, clinical symptoms and signs, clinical diagnosis, treatment, if any, etc., should be at once recorded, with suitable space left for indicating the result of the test.

After the blood has clotted, it should be "rimmed," i.e., a platinum wire or glass rod should be run around between the blood and the tube wall, to separate the clot from the glass. If this precaution is taken, the serum will collect above the clot and may be poured or pipetted off with ease. While the clot is contracting, the tubes should be placed in the ice-chest. It seems hardly necessary to emphasize the fact that extreme care should be taken, not only here, but throughout the test, to prevent bloods becoming mixed or interchanged.

(2) *Preparation of Antigen.*—Obtain a fresh human heart, as nearly normal as possible, being particularly careful to avoid using one showing fatty change. With a pair of scissors, strip the muscle of the ventricles free from the endocardium and pericardium. Weigh the pieces of muscle and grind in a mortar, using clean quartz sand. Add 10 c.c. of absolute alcohol for every gram of muscle and continue grinding until thoroughly emulsified. Transfer the whole to a flask or bottle fitted with a rubber stopper, and shake well. Place in the incubator at 37° C. for from two to three weeks, shaking well each day. Filter through paper into a rubber-stoppered flask or bottle, and add 0.4 grams of pure cholesterolin for every 100 c.c. of extract. Shake well and place in the incubator over night to dissolve the cholesterolin. The antigen is now ready for titration. It should be kept at room temperature, and if a precipitate forms at any time, it should be removed by filtering through paper. Such an antigen, stored in this way in a rubber-stoppered or well-fitting glass stoppered bottle, will keep for many months.

The titration of the antigen is twofold in purpose, first, to determine the power of the antigen to bind the complement of itself, i.e., in the absence of antibody (this is known as non-specific binding, or anticomplementary, power and naturally should be very low in a good antigen); second, for specific binding power. This should be as high as possible.

(a) *For Non-specific Binding Power.*—Dilutions of antigen in saline solution are prepared as follows: 1:2, 1:4, 1:6, 1:8, 1:12, 1:16, 1:20. These are conveniently made by setting up a series of seven tubes in a rack and carefully measuring into each 0.5 c.c. of cholesterinized antigen extract. Then measure the following amounts of saline solution into each tube in succession: 0.5 c.c., 1.5 c.c., 2.5 c.c., 3.5 c.c., 5.5 c.c., 7.5 c.c., and 9.5 c.c. The tubes should then be shaken to mix thoroughly. Place 0.5 c.c. of each dilution in another series of test tubes. Add 3 units of complement and saline solution to make 1.5 c.c. total volume. One may add 0.2 c.c. of pooled negative serum to each tube before adding the saline if desired, although we have found by experience that this is an unnecessary refinement, and does not appreciably influence the ultimate finding as to the value of the antigen.

After shaking, the tubes are placed in the air incubator at 37° C. for one hour. At the end of this time, 1 c.c. of sensitized sheep's corpuscles is added to each tube, and incubation for 1 hour in air at 37° C. is repeated.

The highest dilution in which there are unlysed cells remaining is taken as the anticomplementary power of the antigen. This is sometimes 1:2, but more often 1:4. Antigens giving a higher anticomplementary power are discarded.

(b) *For Specific Binding Power.*—Dilutions of antigen are prepared as follows: 1:30, 1:40, 1:60, 1:80, 1:100, 1:120, 1:140. These are conveniently prepared by setting up a series of seven tubes in a rack and carefully measuring into each 0.1 c.c. of cholesterinized antigen extract. Then measure the following amounts of physiological saline solution into each tube in succession: 2.9 c.c., 3.9 c.c., 5.9 c.c., 7.9 c.c., 9.9 c.c., 11.9 c.c., and 13.9 c.c. Shake each tube to mix thoroughly. Place 0.5 c.c. of each dilution into another series of seven tubes. Add 0.1 c.c. of pooled serum from untreated known cases of syphilis. Also add 3 units of complement, and saline solution to a total volume of 1.5 c.c. Shake well.

Incubate in air at 37° C. for 1 hour.

Now add 1 c.c. of sensitized sheep's corpuscles and again place in the incubator for 1 hour.

The highest dilution of antigen giving complete inhibition of hemolysis is taken as the specific binding power of the antigen. This is usually about 1:120, but often goes higher. No antigen showing a titer lower than 1:100 should be used.

It is thus seen that a good antigen has an extremely wide range between the non-specific binding power and the specific binding power, and it is this wide range which insures the specificity of the test. Such a satisfactory antigen is employed in the actual Wassermann test in a dilution of 1:20, of which 0.5 c.c. is used. In diluting, the antigen is measured into a graduated cylinder, and the saline is added slowly, with repeated shaking, until the dilution is complete. It is important for the technic to be uniform in order to secure consistent results. Antigen must be diluted freshly each day of use.

(3) *Preparation of Complement or Alexin.*—On the evening previous to the day on which the tests are to be made, the guinea pigs are bled by cutting the throat. The animals may be anesthetized with ether, or *slightly* stunned by knocking the head upon the edge of the table. The skin of the throat is cut with a pair of sharp scissors, thus baring the large vessels on both sides of the neck. These vessels are then severed with sharp-pointed scissors, taking care not to cut the trachea and esophagus. The blood is collected into a centrifuge tube or petri dish. A guinea pig of average size should yield sufficient complement for twenty Wassermann tests.

The vessels containing the blood may be left at room temperature for a time to allow clotting to be completed, when the tubes should be "rimmed," as described under Patients' Serum, and placed in the ice-chest over night to facilitate the contraction of the clot. Our experience has been that guinea pig serum, thus obtained, is higher in complement-content than when the animals are killed and the serum used on the same morning. On the day of the test, the tubes containing the guinea pig blood are centrifuged and the clear serum pipetted off. This serum is then diluted 1:10 with physiological salt solution, and is ready for use, without further manipulation.

Such a solution must, however, be titrated for its hemolytic power, for the sera of different guinea pigs vary in their activity in this respect, and no complement must ever be used without being standardized. The procedure is simple: a series of eight tubes are set up in a rack, and into the first is measured 0.05 c.c. of complement (1:10), in the next 0.1 c.c., in the third 0.15 c.c., in the fourth 0.2 c.c., in the fifth 0.25 c.c., in the sixth 0.3 c.c., in the seventh 0.4, and in the eighth 0.5 c.c. Into each tube, excepting the eighth, is then measured 1 c.c. of sensitized sheep corpuscles (*see* page 282), the eighth tube receiving 0.5 c.c. corpuscle suspension only. Each tube is then made up to 2.5 c.c. with normal saline solution. After shaking, the rack is placed in the air incubator at 37° C. for 1 hour, at the end of which time the results are read. The tube containing the least amount of complement which completely hemolyzes the corpuscles is noted. If this is the third tube, it contains 0.15 c.c. of complement (1:10), and this amount is called the *unit* of complement. *Three units are employed in the Wassermann test.* The eighth tube contains no hemolysin, and should show no hemolysis. It is a control to show whether the complement can cause hemolysis of itself. In our experience this practically never occurs.

(4) *Preparation of Amboceptor or Hemolysin.*—To obtain the hemolytic amboceptor, a rabbit is injected repeatedly with washed sheep erythrocytes. It is best to immunize two or three rabbits at the same time, in order to be sure of one being satisfactory, as rabbits vary greatly in their response. Moreover, whether the injections are given intraperitoneally or intravenously, the animals are often found to be sensitive after two or more inoculations, and to die after exhibiting signs of anaphylaxis. For this reason it is better to give small doses at frequent intervals than larger doses farther apart. Although we have ob-

trained serum of high potency by both routes, the author regards the intravenous injections as more satisfactory. One c.c. of solid cells diluted in the syringe with 1 c.c. of saline, and injected intravenously every second day, will usually result in a serum of high titer after from six to eight injections. Healthy, full-grown rabbits should be used.

To test the serum of a rabbit which is being immunized, a small quantity of blood is obtained from the ear of the animal, allowed to clot, and the serum diluted in saline to 1:1000, 1:1500, 1:2000, 1:3000, 1:4000, 1:5000, and higher if desired. A series of test-tubes, one for each dilution, is set up in a rack. In each is placed 0.5 c.c. of the respective dilution. Next 0.5 c.c. of known average strength complement (1:10) and 0.5 c.c. of 5 per cent. washed sheep's corpuscles are added. Each tube is then made up to 0.5 c.c. with saline solution, and shaken carefully. The rack is placed in the air incubator for 1 hour at 37° C. *The titer is taken as the highest dilution which produces complete hemolysis.* A hemolytic serum having a titer below 1:1500 should never be used, and a higher potency is desirable. If the serum of the rabbit which is being tested is satisfactory, the animal should be anesthetized with ether, and bled from the carotid artery into centrifuge tubes, using precautions to prevent contamination of the blood. After clotting, the blood is centrifuged, and the serum pipetted off into small ampules and sealed in the flame. Such ampules kept in the ice-chest will retain their potency for many months.

For actual use, the hemolytic serum is diluted in saline, so as to render measurements of so powerful a reagent more accurate. It is found that a dilution of 1:200 for every thousand of titer is most satisfactory. Thus a serum whose titer is 1:3500 may be diluted 1:700 in saline. These dilutions should be made up every two or three weeks as needed, and must be titrated when made, to make sure that the amboceptor has not deteriorated. To titrate, varying amounts of the dilution, as 0.05 c.c., 0.1 c.c., 0.15 c.c., 0.2 c.c., and 0.3 c.c., are placed in separate tubes, and 0.5 c.c. of average strength complement is added to each tube. Similarly 0.5 c.c. of sheep's corpuscles are measured into each of the series, and the volume made up to 2.5 c.c. with saline solution. The rack is shaken and incubated in air at 37° C. for 1 hour. *The least amount of diluted hemolysin showing complete hemolysis is taken as the unit.* This is usually the tube containing 0.1 c.c. if the dilution is carried out as suggested above. *The amount of hemolysin employed in the Wassermann test is 2.5 units.*

(5) *Preparation of Suspension of Sheep's Corpuscles.*—The blood is drawn from the jugular vein of the sheep with a large bore needle, or may be obtained at the slaughter-house. The flask into which the animal is bled should contain a quantity of sterile glass beads, which are used to defibrinate the blood immediately after withdrawal. This is easily accomplished by shaking the flask vigorously. Upon reaching the laboratory the corpuscles are washed in saline solution until the supernatant fluid is perfectly clear. To do this, a few c.c. of the blood are placed

in each of a number of centrifuge tubes, and saline added to the capacity of the tubes. After thorough mixing they are centrifuged at high speed for ten minutes. The supernatant fluid is then pipetted off and the process repeated as often as necessary. If the proportion of corpuscles to saline is not too great, three washings will suffice. Care must be taken to establish a standard speed and time of centrifuging, particularly for the last washing, as the sedimented cells are the basis for dilution, and if the finished product is to be uniform for all tests at all times, the technic must be uniform. The "solid" cells are diluted in the proportion of 1 c.c. of cells to 19 c.c. of saline, making 5 per cent. suspension. The suspension is now ready for use. It should be placed in the ice-chest until required, and will keep for three or four days. It must not be allowed to freeze.

To prepare sensitized corpuscles: The hemolytic amboceptor is added to 5 per cent. corpuscle suspension in the proportion of 2.5 units of amboceptor to 0.5 c.c. of suspension. Saline solution is added to make 1.0 c.c. The mixture is allowed to stand in the incubator for 15 minutes at 37° C. before using.

(6) *The Wassermann Test Proper.*—Each day, before the actual tests are set up, sensitized corpuscles are prepared and the complement titration is carried out as described on page 280. While this rack of tubes is being incubated, the tubes for the tests are set up and numbered. Each serum to be tested requires four tubes. (A suitable size for these tubes is 4 inches by 0.5 inches, outside measurement. They should be thick-walled.) Into the first is placed 0.2 c.c. of freshly inactivated serum to be tested, in the second 0.1 c.c., in the third 0.05 c.c., and in the fourth 0.4 c.c. Each of the first three tubes then receive 0.5 c.c. of antigen, diluted 1:20 as described on page 279. The fourth tube receives no antigen, as it is the "serum control," being designed to detect any anticomplementary power (non-specific binding) of the serum. All the tubes then receive 3 units of complement. This amount usually the fourth 0.4 c.c. Each of the first three tubes then receive 0.5 c.c. of serum diluted 1:10.

Besides the serum controls just described, there are other important controls necessary in order to fully protect against error. A tube containing 0.1 c.c. of a known syphilitic serum, 0.5 c.c. of antigen and 3 units of complement, must be included with the tests. This in turn requires a serum control tube containing 0.2 c.c. of known syphilitic serum with 3 units of complement but no antigen. Similarly a tube containing 0.2 c.c. of known negative serum, with antigen and complement, must be set up. This requires no serum control, since if it does not show a negative result, it throws out the whole series of tests. Lastly, a control tube to detect anticomplementary action of the antigen must be incorporated. It is true that in preparing the antigen in the first place, this test is included, but each day's diluted antigen must be similarly controlled to detect any deterioration of the stock extract. The antigen control tube receives 1.0 c.c. of antigen and 3 units of complement, but no serum. The latter (a known negative)

may be added if desired, but experience has shown that it is not necessary.

When all the sera to be tested, and all the controls described above, have been set up, the volume in each tube is made up to 1.5 c.c. with saline solution. The racks are then shaken vigorously and placed in the air incubator at 37° C. for 1 hour. At the end of this time, 1.0 c.c. of sensitized corpuscles is added to each tube and, after shaking, the racks are returned to the incubator for another hour. During this period it is well to inspect the tubes from time to time, with occasional shaking. Such inspection often gives the worker valuable information regarding individual tests, as treated cases of syphilis, for instance, may go negative in one full hour, whereas non-syphilitic sera often become completely hemolyzed in 30 minutes.

A positive case shows no hemolysis in the first three tubes. The fourth tube of every test *must be hemolyzed*, or the serum is proved to be anti-complementary, and is not of use for the test. In a negative case all tubes are hemolyzed.

The tube containing the known syphilitic serum should be positive, of course, but its serum control should show complete hemolysis. The negative control serum should be hemolyzed, as should also the antigen control tube. It will be observed that all the controls contain twice as much of the reagent being controlled as is employed in the actual test. This allows a satisfactory margin of safety and is a most important point in the technic.

The following table will serve to simplify the written description and is self-explanatory:

TABLE I.—ACTUAL WASSERMANN TEST

Unknown Patient's Serum	Antigen	Complement	Saline	Sensitized Corpuscles	Results
Tube i 0.2 c.c.	0.5 c.c.	3 units	Up to 1.5 c.c.	1 c.c.	?
Tube ii 0.1 c.c.	0.5 c.c.	3 units	Up to 1.5 c.c.	1 c.c.	?
Tube iii 0.05 c.c.	0.5 c.c.	3 units	Up to 1.5 c.c.	1 c.c.	?
Tube iv 0.4 c.c.	—	3 units	Up to 1.5 c.c.	1 c.c.	Complete hemolysis
Air in incubation at 37° C. for 1 hour					
Known Positive Serum					
Tube i 0.1 c.c.	0.5 c.c.	3 units	Up to 1.5 c.c.	1 c.c.	No hemolysis
Tube ii 0.2 c.c.	—	3 units	Up to 1.5 c.c.	1 c.c.	Complete hemolysis
Air in incubation at 37° C. for 1 hour					
Known Negative Serum					
Tube i 0.2 c.c.	0.5 c.c.	3 units	Up to 1.5 c.c.	1 c.c.	Complete hemolysis
Air in incubation at 37° C. for 1 hour					
Antigen Control					
Tube i —	1.0 c.c.	3 units	Up to 1.5 c.c.	1 c.c.	Complete hemolysis

With this method of performing the Wassermann test, it is found that there are very few sera which yield a non-specific reaction. In making routine examinations for syphilis, however, the rule should be followed that all cases of fixation showing any hemolysis, even in the third tube, must be regarded as non-specific unless the case is in the primary stage or has been treated. Strict adherence to this rule will avoid many unnecessary errors. Sera showing complete inhibition in the first and second tubes with partial or complete hemolysis in the third are regarded in our laboratory as suspicious, and other specimens are obtained from such patients for further testing. Many of these later yield frankly negative or very strongly positive results, showing the doubtful reaction at first obtained to be due to technical error or other causes. All persistent partial positive cases, with the exceptions noted above, are to be regarded as non-specific, unless there are evident signs of syphilis on clinical examination.

As just intimated, the sera of cases of primary syphilis often show a partial fixation, but here the clinical evidence is such as to supplement the laboratory findings and render the diagnosis practically certain. These cases invariably yield complete fixation in a week or two, unless vigorous treatment is instituted. The diagnosis of primary lesions should be sought first of all by means of the dark-field method of demonstrating the presence of *Spirocheta pallida* in the serous exudate from the sore, since positive results may often be obtained by this method, before the Wassermann test shows any fixation whatever.

The technic for performing the Wassermann test upon spinal fluid is essentially the same as that used with serum. The spinal fluid, however, is not inactivated before using, as there is no complement present, and the anticomplementary power is usually very low. The amounts used in making the test are larger than those for serum, being 1.0 c.c., 0.5 c.c., and 0.3 c.c. for the test proper, and 2.0 c.c. for the fourth or control tube. Larger amounts than these may be used so long as the control tube contains sufficient to detect non-specific binding.

The best method of recording the results of the test has been the subject of a great deal of investigation. The method most in vogue is to indicate complete inhibition of hemolysis by four plus signs (++++), and the various degrees of hemolysis by fewer plus signs; thus 75 per cent. hemolysis would be +++, 50 per cent. hemolysis ++; 25 per cent. hemolysis +. If the results in all three test-tubes are to be recorded in this way the method becomes laborious. A most satisfactory means of indicating the exact result has been elaborated by Duncan Graham, who previously was in charge of this laboratory. Each tube showing complete inhibition of hemolysis is indicated by the figure 4. Thus if a serum shows complete inhibition in all three dilutions, it is recorded as 444, or *very strongly positive*. Each 4 represents a separate quantity of the serum, and the three figures indicate exactly as much as if we had written +++++, +++++, +++++. After treatment the third tube may show 50 per cent. hemolysis, while the remaining tubes

still show complete inhibition. Such a result would be recorded 442. The serum of a case under treatment usually undergoes gradually a change from 444 to 000 (negative), as illustrated in the following case:

CASE A. K. UNDER TREATMENT WITH DIARSENOL

Sept. 14, 1917	No treatment	Wassermann 444
Sept. 21, 1917	After one diarsenol	" 444
Sept. 26, 1917	After two diarsenols	" 444
Nov. 2, 1917	After three diarsenols	" 430
Nov. 7, 1917	After four diarsenols	" 320
Dec. 3, 1917	After five diarsenols	" 000

We claim for this method of interpretation that the clinician can see exactly what the technician in the laboratory has found in the test. It is not as cumbersome as the + + + + method, and gives more information. Craig³³ uses only one quantity of serum (0.1 c.c.), and therefore finds the latter method satisfactory. He can only say whether a patient's blood is positive or negative, and cannot detect early change due to treatment, as can be done with a tube containing 0.05 c.c., nor can he follow his treated cases as long as can be done by having one tube containing 0.2 c.c. of serum.

PROBLEMS INVOLVED IN THE STANDARDIZATION OF THE WASSERMANN REACTION.—It is safe to say that of all the laboratory tests now available to the general medical profession, whether chemical, bacteriologic or serologic, none has proved itself of such great value at the present time or offers such great possibilities for the future, as the Bordet-Wassermann reaction. It is quite true that only in the larger centers of population has it had, up to the present, a wide application; and, as a consequence, the statement just made will sound somewhat extravagant to those practitioners from outside points who have not been closely in touch with such work. It is not yet realized by many physicians that syphilis may be the underlying cause of many conditions which are so obscure as regards diagnosis, and so obstinate in yielding to symptomatic treatment.

A wider application of the test would not only reveal the secret in many of these puzzling cases, but would prove of great eliminative value where the result is negative. Add to this the other, larger sphere of this laboratory procedure, that of ascertaining in a scientific and reliable way, the progress of a syphilitic patient under treatment. Too few physicians avail themselves of this valuable guide in treatment and prognosis.

Unlike the Widal test, or other diagnostic methods of the laboratory, the Bordet-Wassermann reaction is complicated in the preparation of the reagents, the carrying out of the technic and the interpretation of the results. It is not to be wondered at, therefore, that many deviations from the original method have been described by various workers, who claim special advantages for their respective modifications. These alleged advantages may be divided conveniently into two classes:

I. Those claiming a more delicate or accurate diagnosis.

II. Those claiming a simplified technic, designed to reduce the labor involved in making the test.

It is not within the compass of this article to describe these various methods in detail, but mention will be made from time to time of some of the important modifications, while discussing the different subjects in their proper order.

It may be well to analyze our objects in performing the Wassermann test. First of all we desire to detect every case of syphilis. Secondly, we consider it equally essential to detect the absence of syphilis in all cases not infected. Extremists are always to be found in the medical profession, and among the champions of the Bordet-Wassermann reaction there are a few enthusiasts who claim for it almost supernatural powers. On the other hand, there are some³⁴ (and their numbers are significantly few) who claim very little specificity for the test. In a calm consideration of the whole matter one must realize that there is no diagnostic method, clinical or laboratory, known to medical science, which is infallible. Not only is there a small percentage of error due to the technic and its limitations, but there is no doubt that the personal element enters largely into the question. As Ottenberg³⁵ says, some good workers obtain satisfactory results in using inferior methods, simply because of skill and experience in using the method.

It is, however, both startling and gratifying to find such an unexpected uniformity of results as now exists in the different laboratories, and this knowledge should act as a spur to encourage the workers to standardize their technic and thus place the test upon the highest scientific plane.

Let us now consider what is involved in the effort to detect every case of syphilis. Viewing the problem from a biologic standpoint, it is not difficult to understand that during the first two, or even three, weeks after the appearance of the initial sore, the test is very often negative in true cases of syphilis. The so-called syphilitic antibody requires time for its production, and it would be unreasonable to expect a positive test before its appearance in the blood. Passing on then to the time when one should reasonably expect the presence of the antibody in the blood, several factors have an important bearing upon the result of the test. Approximately 100 per cent. of all cases of frank secondary syphilis give a positive reaction by any of the well recognized methods. It is in the tertiary and latent stages, as well as in cases involving the nervous system, that diversity of results appear according to the technic employed. To these must be added cases of known syphilis which are undergoing, or have undergone, treatment. One of the most potent causes of this diversity is the difference in antigen used. It is almost universally agreed that a cholesterinized heart-antigen is much more sensitive than a simple heart-antigen. The question we have to decide is, which, if either, is the accurate one? Then, too, comes the strength of the hemolytic system used. It must be decided as to what maximum strength is permissible without danger of losing the delicacy required to detect weakly positive cases. This factor

is just as important as our determination of the minimum strength compatible with safety as regards specificity of fixation. These points, together with details concerning the actual technic employed, are matters which must be left to the judgment of the investigator, and are therefore more or less arbitrary. With these significant facts before us, it is not difficult to appreciate the obstacles confronting an attempt to standardize the whole procedure. It is our purpose to take up each point in detail, to present the actual findings, and to draw, therefrom, conclusions which it is hoped will be of value to the workers in public health laboratories.

For the sake of uniformity we shall assume from the beginning that the total volume in each tube at the end of the reaction is 2.5 c.c. It is true that in the original tests Wassermann used 5 c.c., and it is also true that some laboratories now use very small amounts in an effort to economize in the reagents. Most laboratories now use 2.5 c.c. as the optimum volume, believing that it combines reasonable accuracy with proper economy in reagents. This view coincides with my own personal experience.

(1) *The Antigen*.—As has been intimated above, the question of the antigen is a difficult one to solve. The choice of antigen lies, in the opinion of the great majority of workers, between the simple, alcoholic extract of heart, and the cholesterin-reinforced alcoholic extract of heart. It must be noted, however, that some laboratories, for one reason or another, use the acetone-insoluble fraction of the simple alcoholic extract of heart muscle according to the method of Noguchi. The writer had no personal experience with Noguchi's antigen, and will refrain from comment which would only be based upon second hand information.

The simple alcoholic extract of guinea pig and beef heart has many advocates,³⁶ and with good reason. Ottenberg compares the results obtained with such an antigen with those using a cholesterin-reinforced alcoholic extract. In 95 per cent. of the cases the results were identical. Of the 67 disagreements in 1,241 cases, 42 gave definite positive reactions with cholesterin, and negative or doubtful reactions with the simple antigen. Of these, he says, 22 were cases in which there was no reason to suspect syphilis. Taking the other 25 disagreements, the cholesterinized antigen gave negative results, while the simple alcoholic extract yielded positive tests. Twenty of these were known or highly probable cases of syphilis, while five were doubtful cases in which syphilis could not be excluded. He admits, however, that the cholesterin antigen gives a "far greater number" of weak positive reactions in treated syphilis, though he claims that this advantage is counterbalanced by a considerable number of false positive reactions. He, therefore, draws the conclusion that "cholesterin-reinforced antigen should never be relied on alone for diagnosis."

Let us now analyze the data on which he forms this opinion. First of all, there are 95 per cent. of agreements between the two antigens. Of the 5 per cent. remaining, the cholesterin antigen gave positive reactions in slightly over 3 per cent. of the total, leaving less than 2 per

cent. to the credit of the simple extract. About half of the cholesterin-positive, disputed, cases were undoubted or possible cases of syphilis, which brings the error with that antigen, according to this observer, down to slightly over 3 per cent., as compared with an error of slightly less than 3 per cent. with the simple antigen. So far the advantage is to a very small extent in favor of the latter.

Deduct from this, however, the very important drawback in not being able to detect many cases of treated syphilis. Remember also that 18 of the 22 alleged false reactions charged against the cholesterin antigen were cases of pregnancy which, as has been shown in our laboratory, can easily be ruled out by repeating the test after parturition. Furthermore, where routine tests are made in a large hospital, it is a matter of common experience that many cases of syphilis are latent—presenting no symptoms or signs, and giving no history of infection. Such instances are so common that one is quite justified in concluding that of the twenty-two in which Ottenberg could find no reason to suspect syphilis, some at least were undoubtedly cases of that disease.

Stokes and O'Leary³⁷ find that in nearly every instance of provocative Wassermann tests, the cholesterin antigen alone was successful in detecting positive cases.

One more point is worthy of consideration before leaving this question; namely, the statement already indirectly referred to, that in 25 cases the simple antigen yielded a positive result, while the cholesterin antigen results were negative. No explanation of this phenomenon is advanced, and indeed none suggests itself to me. It seems difficult to understand why an antigen made up in exactly the same way, but with the additional safeguard against false negatives provided by cholesterin, should fail to be as sensitive. Nor has this phenomenon occurred in our laboratory, although it must be admitted that we have not yet made as many tests in parallel as has Ottenberg.

In reporting such a series of cases, it is important to state whether they were done in routine, or in suspected cases. In the former instance there will necessarily be a great many negatives with a correspondingly great number of agreements, while in the latter, there will be many positive tests, with a greater opportunity for the results of the two methods to be at variance. In a series of 300 cases, of which 85 were positive, we found 85 positive with the cholesterin antigen, and 68 with the simple alcoholic extract. All the 68 were found to be among the 85 cholesterin positive cases. Thus 17 cases were negative with simple antigen and positive with cholesterin, and in all these there was no reason to believe they were not syphilitic. Nine had been treated, and two were early primary syphilis. Besides the 17 that altogether escaped detection with the simple antigen, there were 28 in which the reaction, while positive, was weaker with the simple antigen. Of these, 8 had been treated, and 2 others were early cases of primary syphilis.

Of the total 45 disagreements between the two antigens, with one exception, all were in favor of the cholesterin-reinforced extract. In this single exception, a treated case gave a 430 reaction with the simple,

and 320 with the re-inforced antigen. This is the only instance of the kind occurring in my experience, even aside from the series now being reported, and may be due to an error on the part of the technician. Certainly no other explanation seems plausible.

The figures quoted above were obtained by the regular procedure in the case of the cholesterin antigen, and primary incubation for four hours in the ice-chest, in the case of the simple extract. With the ordinary primary incubation of one hour in the incubator the simple antigen gave still less reliable results.

TABLE II.—SUMMARY OF DISAGREEMENTS IN THE NUMBER OF CASES OF SYPHILIS DETECTED BY SIMPLE AND BY CHOLESTERIN ANTIGEN.*

	Cholesterin Antigen	Simple Antigen	Total
Number positive	85	68	85
Treated, but positive	17	12	17
Early chancre, but positive	4	2	4
Reaction strongest (treated cases)	16	1	17

* The figures in this table refer to *disagreements* only. Both antigens were made at the same time, from the same heart. Note how closely the figures in the total correspond to the figures of the cholesterin antigen.

The experience of Thomas and Ivy³⁸ corroborates our own. It may be worth suggesting, therefore, that before such a statement as that of Ottenberg be given full credence, control tests with more than one cholesterin antigen, or duplicate tests with the same antigen, be made, for it is possible that the variance in the results may be due to differences in technic, or even to oversight on the part of the laboratory workers.

To sum up, then, the balance seems to be definitely in favor of the cholesterin-reinforced antigen, to be used, of course, only by experienced workers. There is something to be said, it is true, in favor of using both as a check one upon the other. Here, too, however, it is liable to lead to confusion and doubt in the mind of the worker, who must then decide upon which result he should place his reliance. The author believes that if a worker uses both antigens, the simple antigen should only be considered of value, as *directing his attention* to those cases giving positive results with the reinforced antigen alone, so that he may inquire more minutely into the clinical history, and if desirable, as in the case of pregnancy, febrile conditions and certain tropical diseases, arrange for a further examination of the blood at a later date.

As to the dosage of antigen, the reader is directed, for an admirable summary of the facts concerning this question, to Ottenberg's paper, to which reference has already been made. It is sufficient to say that in our own laboratory the dosage is determined by two main factors, namely, the anticomplementary power, and the specific binding power. No antigen is considered satisfactory which is at all anticomplementary in a dilution of one in six, and which does not give a positive reaction with pooled positive sera in a dilution of one in one hundred. This gives

a wide range, and a point is taken midway between these two extremes, generally one in twenty, of which 0.5 c.c. is used in the test. These remarks apply to a cholesterinized human heart antigen.

(2) *The Alerin, or Complement.*—The next problem to discuss is that of the dosage of the complement. For convenience, it is customary to dilute the guinea pig serum one in ten with saline, and many laboratories use a fixed amount (usually 0.5 c.c.) of this dilution throughout the test. It is true, however, that guinea pig serum varies as to its complement content, and this necessitates the adjustment of the amboceptor to meet the variation. To accomplish this, varying amounts of amboceptor are titrated with a fixed arbitrary amount of complement (0.5 c.c. of 1:10 dilution). Such a method means that instead of increasing the amount of complement when it is weaker than usual, the amboceptor is increased. This procedure is possible owing to the fact that within certain limits the results appear the same. Many laboratories, among them those of Bruck and Citron, follow this method. It seems, however, more reasonable to vary the amount of the reagent, which itself is not constant in quality. We know that the hemolysin is remarkably stable, whereas it is a matter of common experience to find certain guinea pigs whose blood shows a low complement content.

A number of workers, including McIntosh and Fildes, Thomas and Ivy, Walker and Swift, Boas, Ottenberg, use, therefore, fixed amounts of amboceptor, and vary the amount of the complement according to its strength.

The advantage of the former method is one of economy of time, inasmuch as the addition of a complement to the tests need not be deferred until the titration of that reagent is completed. On the other hand, as Ottenberg points out, a weak complement may be supplemented, quite properly, in the second part of the reaction, by an excess of amboceptor, but this still means that during the first incubation (the fixation period) we have a deficient complement as compared with an experiment in which the quality of that reagent is up to the average. So that no matter how one varies the amboceptor, the change does not have the effect of keeping the complement in the test proper at a constant level.

Granting, then, that it is more logical to titrate the complement each day, the question arises as to the method of determining the unit. Wassermann took 1 c.c. of the 1 in 10 dilution, which would bring the amount to 0.5 c.c. in performing the test in half quantities as we prefer. Let us now see how this compares with the results on titrating the complement.

Using an amboceptor which has been titrated and used many times previously with different complements from day to day, the average result of several representative titrations with different satisfactory complements is taken as the unit. This may be 0.1 to 0.15 c.c. of a 1:300 dilution of amboceptor (the amount, of course, varies with the titer of the serum of the rabbit from which the hemolysin has been obtained. If the titer is 1:3000, the dilution should be 1:600). Let

us assume that it is 0.1 c.c. This is called the unit of this particular amboceptor, and is stationary so long as the amboceptor lasts, provided it does not become infected. The unit having been determined, a series of tubes is set up, each containing two and one-half units of amboceptor with varying amounts of complement. If the same complement is used in this test as in the previous one, it will be found that the complement titer will be approximately two and a half times less than the amount used in determining the amboceptor titer. This observation coincides with that of Ottenberg in the earlier part of his paper, but contradicts a later statement of the same author.* The explanation of this apparent inconsistency seems to be that his arbitrary amount of complement is too low to produce the effect to which he calls attention. In other words, it is too near the minimal dose. The author has repeated the experiments he outlines many times and at no time obtained the results he indicates. The following is the nearest the author could get to his findings:

I. Complement 1 in 10, 1 c.c.

Sheep's corpuscles 5 per cent., 1 c.c.

Amboceptor (1-300 dilution of 1-2500 titer.)	0.0	0.05	0.1	0.15	0.2	0.25
Air incubation for 1 hour at 37° C.	N.H.	N.H.	P.H.	P.H.	C.H.?	C.H.*

* N.H., No hemolysis; P.H., Partial hemolysis; C.H., Complete hemolysis.

The unit was, therefore, between 0.2 c.c. and 0.25 c.c., and was taken as 0.22 c.c. Two units of this amboceptor were now titrated against the same complement.

II. Amboceptor 0.14 c.c.

Sheep's corpuscles 5 per cent., 1 c.c.

Complement 1-10	0.3	0.35	0.4	0.5
Air incubation for 1 hour at 37° C.	P.H.	P.H.	A.C.H.*	C.H.

* Almost complete hemolysis.

Thus we see that the unit is 0.5 c.c., or nearly so.

By this it is apparent that the two titrations correspond very markedly, and any difference, while tending toward Ottenberg's contention, is very small.

Our own daily titrations are carried out in much the same fashion. The following is a typical example:

Sept. 7, 1917.

I. Complement 1 in 10, 0.5 c.c.

Sheep's corpuscles 5 per cent., 0.5 c.c.

Amboceptor (1-300 dilution of 1-2500 titer.)	0.0	0.05	0.1	0.15	0.2
Air incubation for 1 hour at 37° C.	N.H.	C.H.?	C.H.	C.H.	C.H.

Unit = 0.06 c.c.

* Ottenberg: Arch. Int. Med., March, 1917. Under the heading, "Methods of Keeping the Hemolytic System Constant," Ottenberg says that one can undoubtedly produce the same hemolytic effect by increasing the amount of amboceptor as by increasing the amount of complement. Later, under the caption "The Dose of Complement," he proceeds to show that 0.6 c.c. of complement will do the same work as 1.0 c.c.

II. Amboceptor two and one-half units (0.15 c.c.).

Sheep's cells 5 per cent., 0.5 c.c.

Complement, 1 in 10.....	0.1	0.15	0.2	0.25	0.3
Reading after 1 hour at 37° C.....	P.H.	P.H.	C.H.	C.H.	C.H.

The unit of complement is thus seen to be 0.2 c.c.

Note how closely Experiment I and II correspond. By multiplying the amboceptor by 2.5, the complement is divided by 2.5.

Variations from this result are infrequent, and are generally minor ones. They probably are caused by slight errors in technic, as for example, allowing a drop or two of complement to escape from the pipet while withdrawing it from the tube.

Having determined the unit of complement in this way, it now becomes necessary to decide the number of units to be used in the test proper, for, after all, this is one of the most important factors in influencing the delicacy of the reaction. Nearly all the workers who do not use a fixed dose of complement employ two units or less. Browning and McKenzie, however, advocate very large amounts—7, 10, 15, 20, 30, 40 units, and Field, 6 to 8 units. These quantities we have found, as have others, to be too large. Two units seem to be very suitable with a simple heart antigen, but with a cholesterinized extract we have found at least 2.5 units to be necessary, while for regular routine 3 units seem advisable, since with the former amount there is sometimes a small amount of nonspecific fixation with certain sera.

The difference between two units as determined by titrating against one unit of amboceptor, and 2.5 units as determined by titrating against 2.5 units of amboceptor, is considerable, so that the actual amounts used by us are somewhat less than those employed by Walker³⁰ and Swift (approximately 12 per cent. less). The reason is found in the fact that by this method we are able to follow the treated cases much further. Two units of complement, as determined by titrating against two units of amboceptor, is actually the same as 2.5 units of complement, as determined by titrating against 2.5 units of amboceptor. Three units of complement, as determined by the latter method (as employed in our laboratory), is equivalent in actual amount of guinea pig serum to 2.4 units, as determined by the former.

The method of Thomas and Ivy theoretically has much to commend it. They use in the test the smallest amount of complement which will give complete hemolysis when titrated in the presence of the regular amount of antigen, and pooled negative serum. In other words, they estimate the anticomplementary power of the serum, and of the antigen serum combination, and arrange for the presence in the test of one unit of complement over and above the amount fixed nonspecifically by these reagents. Ottenberg uses the next dose above that which just gives complete hemolysis, in order to increase the margin of safety.

We have tried this method in parallel with our regular procedure, and must confess that while the results obtained with both were con-

sistent, save in minor details, the readings of our own method were more definite, and while we are still using this modification along with our own for purposes of comparison, we cannot at present feel toward it the same confidence that the regular procedure inspires. It deserves, nevertheless, a longer trial under impartial control before being definitely pronounced inferior.

Before we close this discussion of the complement, mention must be made of a peculiarity of some specimens of guinea pig serum, namely, that they are not nearly so amenable to fixation as are others. Browning and McKenzie showed this in 1909, and Ottenberg also calls attention to it. The latter author has been working at the problem with a view to devising a method whereby the fixability of the complement may be measured in the preliminary titration. Until some such scheme is evolved, the only means of avoiding trouble from this source is by using for each day's test a large number of guinea pigs, thus minimizing the effect, should one of the sera prove weak in this regard.

(3) *Amboceptor Titrations*.—The first question to decide is the length of time to be allowed in the thermostat for the titration. Varying from fifteen minutes (Field, Kaliski), half an hour (Sormani), one hour (Wassermann, Walker and Swift, Thomas and Ivy), two hours (Boas, Thomsen, Noguchi), the time employed by the different workers shows little uniformity. Using the air incubator at 37° C. one finds that hemolysis rarely begins before eight or ten minutes, and while it is more than half completed in thirty minutes, one hour elapses before the process actually ceases. Sometimes, indeed, on leaving the mixtures exposed for a longer period, a further laking occurs, but it is very slight, and it is difficult to see any real advantage in so doing. Shorter periods than one hour are probably justified when using the water-bath, since by that method the tubes and their contents reach the required temperature much more quickly. There is another advantage in the use of the water-bath, namely, that constancy in temperature can be more easily secured, unless, as in our laboratory, a very large incubator is available, enabling one to open the doors without an appreciable change in temperature.

If preliminary sensitization of the corpuscles is carried out in the actual test, it is equally important to follow this technic in the preliminary titration. This may be accomplished by mixing the amboceptor and cells and allowing them to stand in the incubator for fifteen minutes before setting up the test.

(4) *Sheep Cell Suspension*.—Many laboratories obtain their supply of sheep cells from an abattoir and thus are dealing with entirely different corpuscles each day. As has been shown by Ottenberg and Hopkins,⁴⁰ cells of individual sheep vary considerably in their resistance to hemolysis. It would, therefore, seem advisable that one, or if necessary, two sheep be kept for this purpose.

Of more importance is the question of the preparation of the cell suspension. The original method was to wash the corpuscles with saline, by centrifugalization. This was done three times, and after the

supernatant fluid had been pipetted off the last time, the cells were restored to the original volume of the blood by the addition of saline solution. This suspension was then diluted 1 in 20 with saline, making a 5 per cent. emulsion. Some workers, as Browning and McKenzie and Citron, still adhere to this method, but the great majority have discarded it for a modification which seems an improvement. It is merely to make a 5 per cent. suspension of the sedimented corpuscles after pipetting off the supernatant fluid. It is held, and with good reason, that the corpuscle content of the blood of different sheep or even of the same sheep upon repeated bleedings, varies. According to the old method, this would result in varying concentration in the suspensions used. By centrifuging in the same machine at the same speed for a definite length of time, one can obtain a uniform sediment regardless of the corpuscle content of the blood.

An antihuman hemolytic system may be substituted if desired. It does not seem to alter the test in any way, and is often more practicable, especially in small laboratories where the expense of keeping sheep on hand would be out of proportion to the advantage gained.

(5) *Patient's Serum*.—The amount of serum used in the test seems to be fairly uniform throughout the different laboratories. Many use 0.1 c.c. in the test proper, although Wassermann gave 0.2 c.c. as the proper quantity. Personally we follow the method of Boas of employing three tubes containing 0.2 c.c., 0.1 c.c. and 0.05 c.c. respectively. This allows of a more accurate estimation of the strength of the reaction and does not involve a prohibitive amount of labor.

Inactivation of the serum at 56° C. for half an hour in a water-bath is carried out in most laboratories as a routine measure. The objects of this procedure are two: to destroy the complement in the patient's serum, and to remove the unknown substances which render certain sera anticomplementary.

It was also reported⁴¹ that active serum yielded false positive reactions. Noguchi pointed out that this was due to impurities in the antigen, and claimed that active serum used in combination with his acetone-insoluble lipoids precipitated from the alcoholic extract did not give these false positive results. His method, however, has not come into general use, and for the present, at any rate, it seems advisable to adhere to the practice of inactivating the serum.

(6) *Natural Amboceptor in the Patient's Serum*.—It is a matter of common observation that many human sera contain appreciable amounts of antishoop hemolysin, and some contain quite large amounts. Some workers use an extra tube in the test in which they omit the amboceptor, and if laking occurs, they may absorb the hemolysin and repeat the test.

In Noguchi's modification, by using an antihuman hemolytic system, this factor is obviated. We have carried out a considerable number of experiments in regard to natural hemolysin, and have corroborated the statements of Wassermann, Neisser, Bruck, and Schuetz,⁴² and others, concerning its occurrence. We have performed many tests, using the

extra tube for the purpose of detecting its presence, and in all instances of negative results with evidence of a considerable amount of natural amboceptor, the serum was treated with sheep cells, and then the test repeated. In no case in the series was there any difference in the result.

True enough, we not infrequently find evidence of natural amboceptor in the first and second, even in the third tube of the main test, but it seems never to occur in such large quantities as to cause complete hemolysis in a positive serum in the third tube (which contains only 0.05 c.c. serum). Therefore, when we find a test in which the tube containing 0.2 c.c. serum shows partial or complete hemolysis, the second tube showing less hemolysis, and the third tube (containing 0.05 c.c. serum) still less, or none at all, we immediately suspect the presence of natural amboceptor, and proceed to absorb it before repeating the test. Our position regarding the presence of natural amboceptor in the patient's serum is upheld by other authorities, notably Neill,⁴³ who states in a communication published since the above was written, that from his experiments he concludes that the presence of antishoop amboceptor in sera does not yield false results where not less than 0.1 c.c. of serum is used for the test.

Just here it may be well to call attention to some peculiar substance present in some sera, which causes hemolysis in exactly the same fashion, but which is not removed on exposure to sheep cells. Others⁴⁴ have noted the same phenomenon, but so far no explanation has been offered.

(7) *Primary Incubation.*—The majority of workers follow the method of Bordet and Gengou, and of Wassermann, in the primary incubation, that is, one hour in the air incubator at 37° C. In 1913, Jacobsthal⁴⁵ reported that ice-box incubation at 8 to 10° C. for three or four hours gave better results. Since that time, his statements have been confirmed by many others, but lately the matter has come into prominence by the work of Koopman, Ottenberg, and still more recently by Smith and MacNeal,⁴⁶ who find that with ice-box incubation for four hours, the results with simple alcoholic extracts are just as delicate as those with cholesterinized extract in the air incubator at 37° C. We have found the ice-box method to be of decided advantage in using the simple heart extract, and would strongly recommend its use if this antigen is to be employed. The ice-box, however, is quite unsuitable for use with the cholesterinized extract, and as long as we employ this antigen, we shall adhere to the air incubator method.

(8) *The Serum Control Tube.*—According to the method laid down by Wassermann, and followed by the majority of workers, the amount of serum in the control tube is double that contained in the tubes of the test proper, or, as in our laboratory, where there are three tubes, the control contains twice the amount of serum in the first tube (0.2 c.c.). Speaking from a large experience with cholesterinized antigen, I cannot agree with Ottenberg that the control tube containing a double dose of serum does not form an additional factor of safety. If, as I have argued above, the natural amboceptor is not giving us false negatives, his con-

tention that this property of the serum robs it of its value when used in double quantity, does not hold.

The same amount of complement is added to the serum control tube as to the others. Thomas and Ivy, Browning and McKenzie, and Ottenberg question the advisability of this, holding that there is an excess of complement, and thus slightly anticomplementary sera may be taken as weak positives, because the control tube goes perfectly clear. Their contention is probably of importance where their method of using a single dose of serum in the control tube is followed. It is worthy of consideration even where a double dose is used. The means they employ (that of titrating pooled negative sera with complement) to ascertain the anticomplementary power of the serum, so as to measure the minimal dose of complement for the control tube, is open to criticism, for it assumes that the average will suffice, whereas, approximately half the sera will have a higher anticomplementary power than the one given by their test.

The ideal way would be to test each serum for anticomplementary power, and then add just sufficient complement to clear the tube. This, however, would involve a prohibitory amount of time and labor, and the advantage would not justify it.

In our laboratory, it is found that by performing the test with a properly adjusted hemolytic system little difficulty is experienced in this regard. In spite of this, however, there are occasionally a few sera which exhibit a slight inhibition, with the control tube perfectly clear. Where the case is not one of early primary syphilis, or an older case which has been treated, we believe all these slight inhibitions to be non-specific. This view is based on practical experience. We, therefore, never interpret a test as positive unless it is very strongly positive; in other words, unless it shows complete inhibition of hemolysis in all three dilutions of serum.

THE MODIFICATION IN THE STRENGTH OF THE BORDET-WASSERMANN TEST DURING THE TREATMENT OF SYPHILIS.—If the treatment of syphilis involved alone the problem of causing the disappearance of the outward manifestations of the disease, the task would be comparatively simple. Even before the advent of salvarsan, clinicians usually experienced little difficulty in accomplishing, in the average case, a marked clinical improvement, by employing mercury and iodid of potash. With the newer drug the results are often marvelous, inasmuch as under its influence the most extensive lesions frequently disappear in an incredibly short time, and the patient apparently is quite well.

It is not difficult, therefore, to understand how even such an illustrious authority as Hutchinson⁴⁷ should have regarded mercury as a satisfactory and sufficient therapeutic agent. It was not until the discovery by Bordet and Gengou of the antigen-antibody reaction, and its application to syphilis by Wassermann in 1906, that we possessed a scientific means of checking the efficiency of our method of treatment. It is not yet fully realized by many clinicians that while this test is invaluable in the diagnosis of lues, it finds an equally wide and important

field of application in following the progress of the case after the diagnosis has been made and treatment has been instituted. It was not without a considerable degree of concern and even alarm, that the medical profession was informed by this laboratory procedure that in many cases of so-called cures, the disease was far from being eradicated. All statistics regarding treatment had thereupon been rendered out of date and to a large extent useless, and there was ushered in a new era of investigation into the efficiency of the various methods of therapy.

There has appeared since that time a great mass of literature dealing with the effect of treatment upon the strength of the Bordet-Wassermann test. Generally speaking, it is now conceded that the progress of the treatment is gauged most accurately by this test, and a cure is not claimed until the test has been consistently negative for some time, without treatment. So far as these points are concerned the question may almost be considered a closed one. The reason for the investigation here recorded is the fact that many physicians become very pessimistic regarding treatment, after receiving from the laboratory several reports, at reasonable intervals, indicating no change in the test even after prolonged treatment.

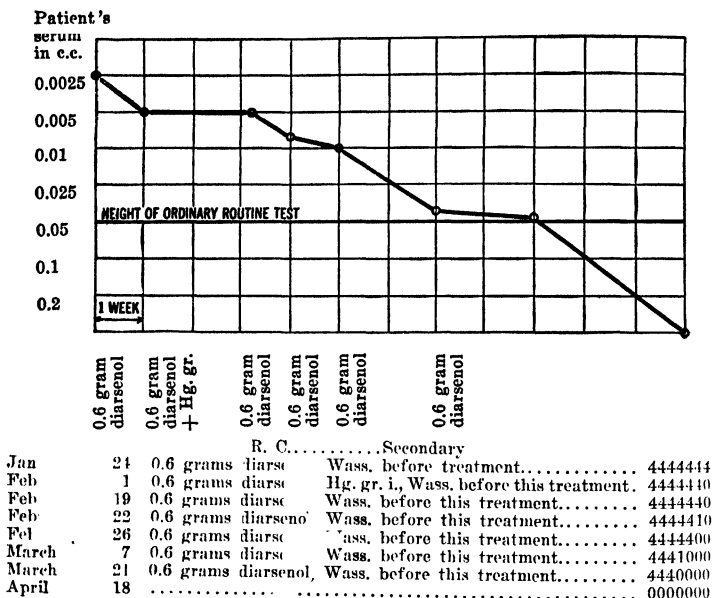
Many cases of syphilis respond readily to treatment—the symptoms disappear, the test becomes negative, and the patient is in all probability cured. There are, however, a great number which do not show any change in the test, or which do so only after a very long and vigorous course of treatment. Out of a large series of cases in the special treatment clinic, 43 per cent., under careful treatment, have shown no change in the test. This percentage is startling, and forms the *raison d'être* of this investigation.

For some time the author has felt that we should know what is going on in these cases during the period of treatment. Are they really receiving no benefit from the administration of antisypilitic remedies? It seemed reasonable that were one able to make a more delicate test of their sera, a change might be detected, even in these apparently intractable cases. In examining the literature we found no report of such work having been done. McIntosh and Fildes⁴⁸ give one or two protocols of cases in whom the sera were titrated somewhat in the manner herein described, but their attention was directed to patients who respond readily. Craig⁴⁹ made dilutions of serum down to 0.02 c.c. in untreated cases, every day for a week, and found that the strength of the reaction varied slightly from day to day. But in the main his results showed that, with repeated tests, the variations are negligible, save in cases which apparently did not have a very strongly positive test at any time. Such instances in untreated syphilis are, in our experience, due to differences in the antigen, or, as suggested by Haller,⁵⁰ to variations in the hemolytic system. The latter author's findings are remarkably constant. Recently King⁵¹ reported results of the quantitative test after treating with salvarsan. In this communication he concludes that little change occurs in the strength of the Wassermann reaction during the first five days following the administration. He

also makes the rather general statement that "some previously untreated cases may be given prolonged salvarsan therapy with very little weakening of the Wassermann reaction." He adds, however, that they may show striking improvement clinically. We shall take occasion to discuss these statements after presenting our experiments and the charts pertaining thereto.

For the purpose of this investigation new cases were chosen, i.e., cases that had never before been treated for syphilis, and they were

FIG. 8.—CASE R. C. CHART SHOWING BORDET-WASSERMANN TEST DURING TREATMENT OF SYPHILIS (SECONDARY).

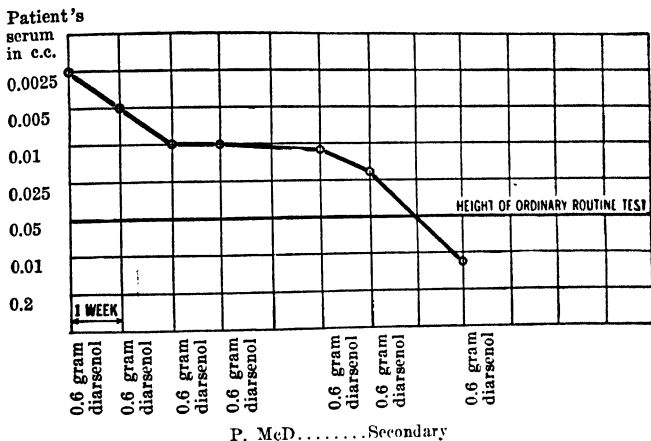


taken in the order in which they came to the out-patient department of the hospital. The number is not large, considering the size of the clinic and the fact that they extend over a period of five months, but many factors come in to disturb an otherwise ideal field. For example, many cases have previously received desultory treatment. Many leave the city before the investigation is completed. Others find that their clinical symptoms clear up, and then, despite the warning of the physician that the disease is not yet eradicated, and the visits of the social service workers in an endeavor to keep them interested in their own cases, they fail to return. The Wassermann test is made before treatment is begun, and then, with few exceptions, every time the patient returns for treatment, a sample of blood is taken just before the treatment is adminis-

pared. This means that the majority have a weekly test. The same antigen is used throughout the series. The serum in all cases is diluted, so that the small amounts to be used may be accurately measured. Seven tubes beside the serum control are used for each case, and they contain 0.2 c.c., 0.1 c.c., 0.05 c.c., 0.025 c.c., 0.01 c.c., 0.005 c.c., and 0.0025 c.c. of the patient's serum. The control tube contains 0.4 c.c.

There are 75 cases in the series. Of these, 5 are congenital, 10 are in the primary stage, 24 in the secondary stage, 26 tertiary, and 4

FIG. 9.—CASE P. McD. CHART SHOWING BORDET WASSERMANN TEST DURING TREATMENT OF SYPHILIS (SECONDARY).



January	17	6 grams	diarsenol,	Wass. before treatment	444444	
January	24	6 grams	diarsenol,	Wass. before this treatment	444440	
February	1	6 grams	diarsenol,	Wass. before this treatment	444400	
February	7	6 grams	diarsenol,	Wass. before this treatment	444310	
February	19	6 grams	diarsenol,	Wass. before this treatment	444300	
February	22	6 grams	diarsenol,	Wass. before this treatment	444100	
March	7	6 grams	diarsenol,	Wass. before this treatment	330000	
March	21	Hg. Sal.,	Wass. before this treatment		330000	
June	13	Hg. Sal.,	Wass. before this treatment		110000	

latent. In 6 the stage is not known.* These 75 cases were taken consecutively as they presented themselves at the clinic, the only restrictions exercised in their selection being that they must have a strongly positive Wassermann test to begin with, and must never have had treatment for syphilis before.

Of the 75 cases, 18 have become negative. Of these, 2 are congenital, 5 secondary, 4 tertiary, while 1 was a case of latent syphilis. The

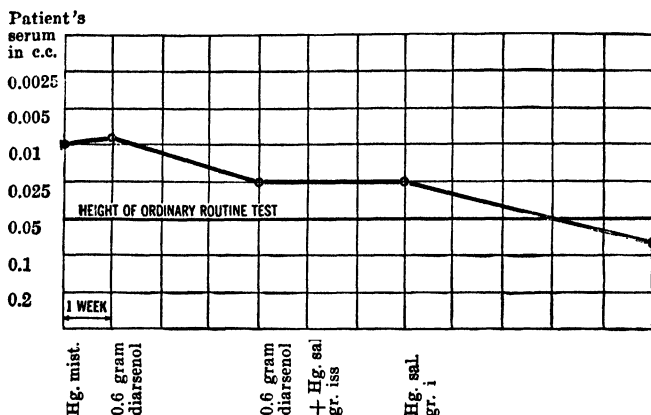
*Owing to the lack of a clear line of demarcation between the different stages of syphilis, the above classification is necessarily arbitrary and only approximate. "Primary" means the presence of a chancre. "Secondary" means the presence of a rash, sore throat, mucous patches, condylomata, etc. "Tertiary" means the presence of gummata, vascular changes, etc.

average amount of treatment required to produce these negative tests was five doses, averaging 0.5 grams (8.0 grains) of diarsenol.

Of the 75 cases, 60 have definitely improved from a serological standpoint, leaving fifteen unimproved. In analyzing the 15 the author finds that only 7 of them had more than two injections of diarsenol; 1 of the 7 had only three injections, while of the 6 remaining, one is a congenital case, and 5 are old tertiaries.

It is impossible to compare our results with those of any other in-

FIG. 10.—CASE M. L. CHART SHOWING BORDET-WASSERMANN TEST DURING TREATMENT OF SYPHILIS (TERTIARY).



M. L. Tertiary

November	10	Mixed treatment, Wass. before treatment.....	4444400
November	18	6 gr. diarsenol, Wass. before treatment.....	4444410
December	11	6 gr. diarsenol + Hg. Sal. gr. iss, Wass. before this treatment.....	4444000
January	4	Hg. Sal. gr. i, Wass. before this treatment.....	4444000
April	18	Hg. Sal. gr. i, Wass. before this treatment.....	4410000

vestigator, because of the lack of parallel experiments. King probably comes the nearest to our field of work, but he observed his cases over a very short period of time—five days. He concludes that very little change occurs in the strength of the Wassermann test as the result of a dose of salvarsan. In looking over his protocols we find that three cases out of twenty show a definite weakening of the test, and while ours show a higher percentage than this, we agree to a certain extent with his contention that it takes more than one dose to produce a marked effect on the alexin-fixing substances. It was a serious mistake at the beginning of salvarsan therapy to assert that one dose, or at the most two, would be sufficient to cure. It is not surprising to find the laity reluctant to discard this hope, in view of the fact that the symptoms and lesions often clear up rapidly. But that many of the profession

should also be slow to acknowledge its fallacy is indeed a matter for concern, for it is surprising how many still treat syphilis without calling in the aid of the laboratory to ascertain the progress of the case.

The charts are shown with the view of impressing upon our minds the optimistic outlook in treating syphilis. What we wish specially to bring out is the fact that in nearly every case, long before the ordinary Wassermann test shows any sign of being affected by the treatment, the more delicate titration of the serum herein described gives unquestionable evidence of benefit. This is well shown in a graphic manner in the charts appended. These charts are type cases, and serve to illustrate our contentions in a much less laborious manner than that of writing out in full the experiments undertaken. Besides the charts, there are several examples of actual protocols. These are included not so much because they are essential to the full report of a case, as because they serve to illustrate our method of recording the strength of the test by figures representing the degree of inhibition of hemolysis.

Among the cases which have not responded to the treatment, there seems to be no real cause for pessimism, save in a very few instances of long-standing tertiaries. Even these may show decided improvement before the treatment is abandoned. None of them have had more than eight doses of diarsenol, and there are very few clinicians who would consider that number a fair test of a therapeutic measure. This view is based on practical experience, for we have seen many instances where the patient required more than twenty doses to produce a change in the Wassermann test.

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CHAPTER VIII

FOCAL INFECTIONS

By JOSEPH S. EVANS, M.D.

Introductory, p. 303—Defenses of the body against bacterial invasion, p. 304—Localization of invading bacteria, p. 307—Common sites of etiologic focal infections, p. 321—Focal infections of the nasal tract, p. 321—Tonsillar foci of infection, p. 324—Aural focal infections, p. 325—Oral focal infections, p. 326—Lymph-node focal infection, p. 327—Pulmonary focal infection, p. 328—Etiologic foci of infection in the gastro-intestinal tract, p. 329—Etiologic foci of infection in the genito-urinary tract, p. 330—Skin focal infections, p. 331—Acute and chronic diseases secondary to focal infections, p. 332—Heart and pericardium, p. 334—Serous membranes, p. 336—Joints and bursæ, p. 337—Skin manifestations, p. 343—Acute and chronic infections of the gastro-intestinal tract, p. 344—Eye infections, p. 348—Thyroid gland, p. 349—Genito-urinary tract, p. 350—Infections of the nervous system, p. 351—Infections of muscle tissue, p. 353—Infections of bone tissue, p. 354—Toxic effects of focal infections, p. 355—Diagnosis of focal infections, p. 356—Clinical history, p. 358—Special examinations, p. 359—Laboratory examinations, p. 361—Treatment, p. 364—Prophylaxis, p. 364—Curative treatment, p. 365.

INTRODUCTORY

The term *focal infection* does not define a clinical entity but rather describes the bacteriological, pathological, and chemical processes involved in the invasion and localization of pathogenic bacteria in the body. The etiologic relation of pathogenic bacteria to infectious diseases, both local and general, has been definitely established by the development of bacteriology, while the more careful coördination of clinical observation and laboratory experimentation during recent years has explained much of the mechanism of such infectious processes and the relation of localized infections to systemic diseases.

A *focus of infection* is a circumscribed region in which pathogenic microorganisms multiply within the tissues. It is because of this localization in the tissues that it is spoken of as a focalized or focal infection. In other words, it is the point at which a definite pathological process has been established and, as has been shown clinically and experimentally, is a region in which agencies arise which may produce changes in the function and structure of any organ or tissue in the body. A focus of infection may be either *acute* or *chronic*, from the standpoint of the local pathological process, or *transient* or *persistent*, from the standpoint

of duration. It may exist with or without demonstrable local or systemic disturbances. In order properly to diagnose the existence of a focus of infection, to determine its etiologic relation to an existing local or systemic disease and to apply rational therapeutic measures, it is necessary to understand the factors involved in the defense of the body against primary bacterial invasion and against such infecting agents subsequent to invasion.

DEFENSES OF THE BODY AGAINST BACTERIAL INVASION

These are primary and secondary. The primary defense depends upon the integrity of the epithelium of the skin and mucous membrane and the chemical nature of the surface fluids. The secondary defenses reside in the cells of the deeper tissues and the intercellular fluids including the lymph and the blood. The white blood-corpuscles and the tissues of the lymphatic glands seem to be especially concerned in these defenses. In part the cells react by ingesting and digesting invading microorganisms, a subject first developed by Metchnikoff under the term "phagocytosis." In part the defenses are made manifest by biochemical reactions, the production of various types of "antibodies" such as "antitoxins," "bactericidins" and the like, which are more fully described in the section on Immunology. In part the defenses are manifested by tissue production designed to "wall off."

Primary Defenses.—The presence of a bacterial flora on the surface of the skin and the mucous membranes, even though the latter may line an inner cavity of the body, is not an infection of the body. The presence of the varied forms of pathogenic microorganisms in the nasal and oral cavities does not necessarily mean that an infection exists. It is only when the integrity of the epithelium is destroyed, thereby permitting invasion by those organisms, that infection occurs. The integrity of the epithelium depends not alone upon its structural continuity but upon the normal physiological function of the constituent cells. The experimental observations of Von Klecki—that microorganisms may pass through the apparently intact intestinal mucosa—and of Wood—that the anthrax bacillus entered the parenchyma of the tonsil through living unaltered epithelium lining the crypts—are based entirely upon the question of the anatomical, not the physiological, integrity of the epithelium. The factors involved in the maintenance of normal physiological function of the cell, as far as is known, are those concerned in the general problem of enzymic activity. Burge has shown that the epithelial cell possesses a definite zymotic (fermentative) action especially in its outer portion. Our present conception of the rôle played by ferments in the production of immunity against pathogenic bacteria indicates the probable relation of this property of the epithelial cell to resistance against primary bacterial invasion. The resistance of the surface epithelium frequently is aided, also, by the chemical nature of the surface fluid, like the acid urine in the bladder.

PORTALS OF ENTRY.—When a break in the integrity of the epithelium, either anatomical or physiological, occurs, it is spoken of as a *portal of entry*. A *portal of entry* may occur at any place in the skin or in any of the mucous membranes, such as that of the eye, of the middle ear, of the respiratory, digestive and genito-urinary tracts, but the frequency of such invasion depends upon factors which are of importance in the determination of the probable localization of an infection, since it is at or near such points of entrance that primary focalization occurs.

The factors involved in the development of portals of entry are: (1) degree of structural and functional resistance of the protecting integument; (2) frequency, extent and duration of exposure to infecting agents; (3) frequency, extent and duration of exposure to mechanical trauma; (4) the nature and the number of the bacteria to which the surface is exposed, as a factor in physiological trauma; (5) factors favoring the development of bacteria, both in number, degree of virulence, and specific pathogenicity (temperature, moisture, food and oxygen supply, and tissue reaction).

The degree of structural and physiological resistance is greater in the skin than in the mucous membrane, due to added protection of the corium and to the cornification of the epithelium. The frequency, extent, and duration of exposure to infecting agents and to mechanical trauma is greater in the mucous membrane surfaces. The physiological traumatization of the epithelial cell apparently is more common in the mucous membrane as evidenced by the incidence of invasion. It may be a part of a general decrease in body resistance or, as has been suggested, a lowering of the functional activity of the local cell by the specific invasive property of the bacteria upon its surface. It is recognized that the *Treponema pallidum* may invade the uninjured mucous membrane of the lip and that the gonococcus may invade the mucous membrane of the conjunctivæ, while these membranes are particularly resistant to other infections. This evidence of specific invasive property of bacteria, therefore, may be an important factor in decreasing cellular resistance by disturbing the balance of cell metabolism. The invasive property of bacteria apparently is not dependent necessarily upon the degree of virulence. Virulent organisms usually do invade and overcome the resistance of the cell with great rapidity, but at times such organisms may lie on mucous membrane and skin surfaces without evidence of disturbances of cellular activity. On the other hand, avirulent micro-organisms may invade apparently normal protecting cells, producing secondary lesions in the body without evidence of increasing their virulence to animals, though the specific tissue pathogenicity of such organisms may be more or less constant. This is well illustrated by the studies of Schottmüller, Billings and Rosenow in chronic infectious endocarditis which they found to be due to a streptococcus of such low virulence that animal experimentation was difficult, but with a specific pathogenicity in the production of endocardial lesions.

The optimum conditions for the numerical increase and the development of special characteristics in bacteria exist in the warm, moist

cavities of the body lined by mucous membrane. Therefore, the factors favoring the entrance of pathogenic microorganisms are especially frequent in the upper respiratory and upper digestive tracts. Clinical experience shows that nasal and throat infections are the predominant infections of young adult life. In a study of the morbidity of young adults at the University of Wisconsin, in 3,900 instances clearly defined evidence of acute bacterial invasion was noted. Of these, 57 per cent. were nasal, 22 per cent. tonsillar, 17 per cent. oral, 2.75 per cent. skin, 1 per cent. genito-urinary and .25 per cent. anal.

While such a relative incidence of invasion might not obtain in a group of individuals living under different social, moral and hygienic conditions, and at a different age period of life, it does illustrate the great preponderance of nasal, pharyngeal and oral infections. Relative incidence of invasion does not determine necessarily the relative incidence of focalization in a corresponding region, but focalization is apt to take place at or near the portal of entry. It is important to recognize these facts clinically, for it is during childhood and young adult life that prophylactic measures are necessary if we are to prevent those progressive degenerative changes that manifest themselves after middle life as the result of previous invasion and focalization of pathogenic bacteria.

Secondary Defenses.—Following the primary invasion of bacteria, the secondary defenses are called upon to protect the body. These defenses, as already pointed out, are chemical, biochemical and morphological, brought into play by the *process of inflammation*. The invading organisms probably are first antagonized by the chemical action of the intercellular fluids. If they survive, tissue reaction occurs in response both to the irritation of a foreign body and to the stimulation of the cells by the bacterial toxins. The positive chemotaxis of most bacterial endotoxins attracts the leukocytes, lymphocytes and tissue cells to the site of invasion. Phagocytosis occurs, there is the liberation of the endotoxins which stimulate the body cell to the overproduction of bactericidal substances. If this reaction is sufficient, the infection is overcome; but if insufficient, the process of "*walling off*" takes place. With the failure of the ingestive, digestive and chemical processes to destroy the bacteria completely, tissue growth attempts to prevent contiguous invasion. Circumscription of infection, therefore, is an evidence of a defect in the secondary defenses of the body, for while the confining wall usually prevents further extension of the infecting agents into the surrounding tissues, the organization of this tissue growth with its newly formed blood supply predisposes to bacterial invasion of the blood system. This is illustrated in Fig. 1. Therefore, dependent upon the degree of virulence of invading pathogenic microorganisms and the degree of body resistance, either an acute secondary invasion or a primary focalization may occur.

When the virulence of the infecting agent is exceptionally high and the resistance of the tissues exceptionally low, there is, as described by Adami, a *fulminating infection*, "in which from the onset to the conclu-

sion the tissues are unable to overcome the virus." Such infections are frequently seen during the puerperium and in such virulent streptococcal infections as the milk-borne epidemics described by various authors.* In the puerperal infections, the lessened body resistance is usually the predominant factor. The bacterial invasion probably usually occurs through a break in the structural integrity of the protective covering of the genito-urinary tract, but there are some instances in which a previous low grade bacteriemia, arising from a persistent focus of infection elsewhere in the body, has been the underlying cause of the puerperal sepsis, the bacteria finally lodging in the injured tissues of the genital tract, gaining increased virulence and overcoming the general defenses of the body. In the milk infections, the fulminating infections probably depend most frequently upon the extreme virulence, pathogenicity and invasive property of streptococci grown in milk either from human source or from a mastitis.

When the body resistance is more nearly proportionate to the degree of virulence of the infecting agent, there arises an *acute infection* in which "while at first the tissues lack that degree of resistance necessary to completely destroy the microorganisms, they are stimulated by the infection and eventually neutralize the effects of the bacteria and their toxins." Such self-limiting diseases as the acute exanthemata, pneumonia, and typhoid fever, are examples of this type of invasion. It is of clinical importance to bear in mind, however, that though the reaction of the tissues may overcome the general acute infection, the tissues themselves may, in many instances, develop a peculiar sensitiveness to infection which predisposes to the invasion and localization of less virulent bacteria. This is evidence of a defect in the biochemical defenses which permits circumscription.

Whenever the morphological and chemical defenses of the body possess a higher degree of potency than the degree of virulence of the invading microorganisms, either the latter are entirely destroyed or are localized in a circumscribed area of tissue, a *focus of infection*. Fortunately, the former is the common occurrence, for the destruction of the integrity of the protecting integument is so frequent that the incidence of invasion is out of all proportion to the incidence of focalization. At the same time with the development of methods of precision in diagnosis, especially in the use of the x-ray, the incidence of localized infection is found to be far greater than the incidence of general infection or of demonstrable systemic disturbances secondary to that infection.

LOCALIZATION OF INVADING BACTERIA

The localization of pathogenic bacteria in the body depends, as already stated, upon the secondary defenses of the body, the leukocytes, the lymphatics, and those indefinite chemical processes which stimulate the cells and fluids of the body to counteract disease-producing agents.

* Capps and Miller; Davis; Hamburger; Henika; Rosenow; Winslow.

There are two stages of localization: first, the primary focalization, which occurs at or near the point of entry, and second, the secondary focalization, which may occur at any tissue or organ of the body. Secondary focalization may occur by invasion or localization in the lymphatics, *lymphogenous focalization*, or by invasion of the blood-vascular system and localization in any tissue supplied by that system, *hematogenous focalization*.

PRIMARY FOCALIZATION

Types of Invading Organisms.—Primary focalization depends upon the immediate localization of invading bacteria in the tissues at or near the point of entry. These infecting agents may be of any type. The *Bacillus tuberculosis*, the *Treponema pallidum*, the *Bacillus typhosus*, the *Bacillus coli communis*, the members of the streptococcus-pneumococcus group, the *Micrococcus pyogenes*, the *Micrococcus catarrhalis*, the *Bacillus influenza* and the diphtheroid organisms are the most frequent etiologic agents encountered in focal infections, but any form of pathogenic bacteria may produce lesions, both primary and secondary, that are focal in character. In this chapter, however, it is mainly to the members of the streptococcus-pneumococcus and diphtheroid groups that special consideration will be given in the study of this problem.

Relation of Primary Focal Infection to Local and Systemic Diseases.—That foci of infection in the body have an etiologic relation to systemic diseases has been established by abundant clinical and experimental evidence. Many of the diseases formerly considered to be due to metabolic faults and classified as "constitutional disturbances" due to some "diathesis" or "dyscrasia," have been proved to be due to infections.

The effects secondary to a focalized infection may be either *immediate* or *remote*, and the pathological processes either *acute* or *chronic*. The occurrence and character of the secondary manifestations depend upon: (1) The number, virulence and specific pathogenicity of the bacteria contained in the focus; (2) the degree of tension in the focus due to mechanical obstruction to natural drainage; (3) the degree of vascularity of the focus.

Foci containing large numbers of virulent pathogenic bacteria so located that natural drainage is difficult or completely obstructed—with marked vascularity caused by new loops of blood-vessels thrown out in the protecting wall and with an imperfect wall thrown up by the morphological defenses of the body—produce immediate and acute secondary systemic manifestations; the reverse conditions existing, remote and chronic conditions arise.

Immediate acute manifestations are readily recognized as being related to the primary invasion of an infecting agent, provided the pathology of the secondary lesion is understood. The relation of acute tonsillitis to acute rheumatic fever and simple endocarditis has been generally recognized, since the original communication of Poynton and Paine, and is an example of the acute manifestations arising immediate

to tonsillar focalization. Recent laboratory evidence and clinical observation has established the infectious character of many other acute diseases and their direct relation to preëxisting foci of infection. These conditions will be discussed later individually.

The relation of persistent foci of infection to secondary chronic systemic manifestations and to the predisposition to recurrent acute systemic diseases is not so generally understood or accepted. A focus of infection may and does frequently persist without producing either noticeable local or general symptoms, but such foci are always sources of potential danger not only from the standpoint of further bacterial invasion but from the standpoint of the disturbance of the stability of the defenses of the body against infection in general.

It is probable that such foci in some instances increase the natural immunity of the individual against bacterial invasion in a manner similar to the reaction produced by the injection of dead bacteria as a prophylaxis against disease, for example, prophylactic typhoid inoculation. Immunization with specific foreign protein, however, depends mainly upon the introduction of the proper amount to produce a "positive phase" reaction. In the more acute types of localized infection such a reaction may take place, but in the lower grade of infections it is more probable that the endotoxins, either absorbed from the focus itself or produced in the blood system by the destruction of non-virulent organisms which have invaded it, cause a particular sensitization of the tissues that predisposes to a lessened resistance against bacterial invasion, a tissue hypersusceptibility. This tissue reaction may be closely related to Wright's "negative phase," but no such determination has as yet been made.

The experimental studies * with anaphylaxis show that foreign protein introduced into the body parenterally is split up by enzymic action and that the products of cleavage stimulate the cells to overproduction of enzymes. Such a mechanism implies hypersusceptibility. Clinical observations ** as to the etiologic relation of foci of infection to anaphylactic reactions show that the bacterial endotoxins invading the system from a confined area of infected tissue act in a similar manner in causing a specific tissue hypersusceptibility.

The hypersusceptibility to acute infections following the artificial introduction of bacterial endotoxins is suggested by a recent personal observation. In a unit of 400 men there occurred an epidemic of throat infection due to the *Streptococcus hemolyticus*, five days following the administration of prophylactic typhoid vaccine. One hundred and eighty-eight of these men manifested systemic reaction to the streptococcus infection during a period of 36 hours. The incidence of this acute infection was 22 times greater in those individuals receiving prophylactic injections of foreign protein than in those, living under similar conditions, who did not receive such treatment.

* Auer and Lewis; Jobling; Longcope; Park; Rosenau and Anderson; Theobald Smith.

** Meltzer; Vaughan; von Pirquet; Weil.

A similar hypersusceptibility probably occurs as a part of the process of the body reaction against an acute infectious disease, which predisposes to bacterial invasion from persistent foci of infection of low virulence. In scarlet fever, for example, the *Streptococcus hemolyticus* is found invading the mucosa of the nasopharynx, as shown by Anthony and by Tunncliffe. The same organism may be demonstrated in the immediate lesions complicating the fulminating type of the infection. When normal tissue reaction occurs, the general infection is overcome and there is a critical subsidence of symptoms, the patient being in the state of convalescence. There frequently occurs, however, sometimes during convalescence and sometimes even weeks and months after apparently complete recovery, those complications which make this one of the serious diseases of life. Simple vegetative endocarditis and nephritis are common late sequelæ, as well as frequent complications during the period of generalized infection. It has been noted, however, that when general infection subsides there is apt to be a subsidence of the endocardial and kidney infections that have occurred during the course of the disease. This is not true, however, when these conditions occur as sequelæ. It is interesting to note that while the *Streptococcus hemolyticus* is in some way associated with the immediate acute manifestations of scarlet fever it is the *Streptococcus viridans*, an organism of less virulence, which is the type isolated from the late lesions occurring in the endocardium and in the kidney. Whatever the actual process involved may be, this common clinical experience indicates the importance of definitely determining the presence of latent infections following these acute invasions and of carefully removing them whenever possible. As long as a suppurative otitis media, a tonsillitis, an adenitis, or a low grade inflammation of the accessory sinuses of the nose persists, following scarlet fever or any of the other acute infections, the patient is menaced by the possibility of secondary complications.

That individuals harboring chronic foci of infection are similarly sensitized and less resistant to acute infectious diseases during young adult life has also been the experience of the author. In observing the morbidity incidence in over 23,000 adults during the past eight years it was noted that the incidence of acute invasion by bacteria, as evidenced by the epidemic form of pyogenic infections of the upper respiratory and upper digestive tracts, was greater in those individuals who exhibited evidences of a persistent low grade infection of the nasal accessory sinuses or of the tonsils than was the incidence of similar infection in those individuals free from such persistent nasal and throat infections. It was also observed in those individuals in whom such persistent infections were subsequently corrected that the incidence of acute bacterial infections was diminished. Crowe's observations support this experience. He observes that patients with tonsils damaged by previous infection or partial operation are more apt to have systemic disturbances following either an acute or chronic tonsillitis than are those with apparently normal tonsils.

In this regard it is also interesting to note the observations of IROBES

and Marine at Camp Custer in the winter of 1917-1918 as evidence not only of the sensitization of tissues by previous bacterial infection but of the apparent development of specific tissue affinity on the part of bacteria. During December, 1917, there were two hundred cases of measles and fifty cases of rubella in the base hospital. Only three cases developed secondary complications, otitis media. Late in December and early in January, nose and throat infections became prevalent throughout the cantonment in the form of "colds," acute bronchitis, pharyngitis, and tonsillitis. Following this period of acute infections of the upper respiratory and upper digestive tracts, those patients with measles, as well as those with other acute infections, developed serious and frequently fatal complications involving especially infections of the serous membranes. Alexander reported somewhat similar observations from Camp Zachary Taylor during the same period.

These instances which are clinical evidences of the development of lessened resistance, due to protein sensitization by bacterial endotoxins, have been substantiated by the laboratory experiments of Rosenow which were later confirmed by Davis, who showed that extracts of the *Streptococcus hemolyticus* sensitized guinea pigs to extracts of pneumococcus and *Streptococcus mucosus*, and vice versa. They also suggest that this continued sensitization of tissue by the endotoxins is one of the important factors governing the development, *in situ*, of specific pathogenic affinity on the part of bacteria confined in foci of infection.

Mode of Dissemination of Bacteria from Foci of Infection. - As has just been pointed out, primary foci may influence the general powers of body resistance without giving rise to any well-marked secondary bacterial invasion of the body. Frequently, however, bacteria from the primary focus get into the lymph or blood streams and then are transferred to other regions of the body where again they may be localized, giving rise to *secondary* foci of infection.

As the lymphatics play an important rôle in the defensive mechanism against infection, the incidence of LYMPHOGENOUS invasion is high. In the majority of cases, however, the invading bacteria are overcome in the lymphatic system. In other instances, the organisms become localized in a lymph node and then play the same rôle as does the primary focus at the point of entry. Therefore, the prevalence of etiologic lymph node infection is relatively common. When the virulence of the organism is high as compared to the general resistance of the body, further invasion may occur by extension through the lymph channels into the blood stream. There is also some evidence that lymphatic invasion takes place against the normal direction of the lymph current. Secondary hematogenous invasion through the lymph channels is seen in the virulent streptococcus infections of the subcutaneous tissues associated with lymphangitis, lymphadenitis, with rapid invasion of the blood stream and the production of multiple secondary infections throughout the body. Lymphatic infection is not always due to direct invasion from the primary focus, but may occur secondary to invasion of the blood-vascular

system, the lodging of bacteria in the lymphatic gland being the result of hematogenous metastasis.

The HEMATOGENOUS invasion from the primary focus is the most frequent type, according to the evidence at hand from laboratory experiments. As previously stated, the pathological process involved in the primary "walling off" of the invading bacteria predisposes to this type of invasion. The new loops of blood-vessels forming the increased vascularity to supply the cellular tissue attracted to the point of invasion by the positive chemotaxis of the bacteria and their endotoxins

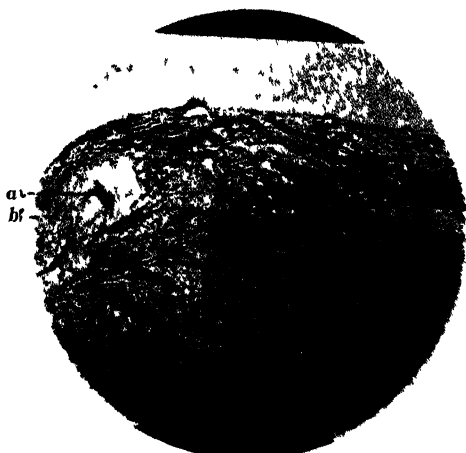


FIG. 1, A.—GRANULOMA FROM ROOT OF TOOTH, SHOWING THE DENSE FIBROUS WALL SURROUNDING THE POINT OF INFECTION (a) WHICH LIES CLOSE TO NEWLY FORMED CAPILLARIES AT ITS APEX (b).

Protection against contiguous invasion is well developed, but the proximity of the infected region to the blood-vessels predisposes to invasion through the blood vascular system (E. C. Rosenow. Gram-Weigert stain).

are thin-walled and permeable upon increased tension. This fact is well illustrated in Fig. 1, which shows a dental granuloma containing a persistent focus of infection. While such a granuloma gives local protection from direct extension to contiguous tissues, because of the thick wall of fibrous tissue, it differs from the granulation tissue of the healing by second intention in that the leukocytic defenses have failed. It may be, therefore, that the inadequate drainage in such a confined area of infection predisposes to invasion of the newly formed blood-vessels that supply this inflammatory tissue, because the leukocytes within the capillary loops fail to overcome the invading bacteria. In this figure the nest of streptococci is seen surrounding the blood-vessel. The

thick fibrous wall gives ample protection to the surrounding tissues, so that if drainage does occur it must be through the blood-vascular or lymph-vascular systems. It is, therefore, seen that while granulation tissue forms a protecting wall between infected and non-infected tissue, its newly formed vascular supply is a point of least resistance.

Hematogenous invasion is *embolic* in character. The invading organisms circulate through the blood-vascular system in a manner similar to the organic emboli thrown off from a thrombus or vegetation and are carried to the terminal branches of that system. If they are in suf-



FIG. 1, B.—PHOTOMICROGRAPH SHOWING MASS OF STREPTOCOCCI IN AREA *a* OF FIG. 1, A (E. C. Rosenow. Gram Weigert stain).

ficient number and possess a certain quality of virulence, they lodge in the tissues producing an anatomical reaction similar to that which occurs at the primary point of entrance. In *acute* hematogenous invasion the bacteria invade the tissue directly from the blood stream and set up an acute inflammatory process, but in *chronic* secondary focalization the process is similar to embolism with infarction. The primary reaction of chronic secondary focalization is an endothelial proliferation of the intima of the blood-vessels followed by a triangular area of hemorrhage secondary to the blocking of the blood-vessels. The bacteria lodge in this hemorrhagic area and through their positive chemotactic influence attract the leukocytes and endothelial cells. There is experimental evidence that bacteria invading the tissue in this manner are apt to undergo lysis, the endotoxins causing tissue reaction and proliferative fibrosis. This is the type of process involved in some of the chronic forms of arthritis where a primary focus of infection is con-

stantly feeding the periarticular tissues, the fibroid changes progressing as the result of continued invasion and lysis of the bacteria with secondary tissue irritation. Adami describes this process as "subinfection."

SECONDARY FOCALIZATION

Site of Secondary Focalization.—The point at which secondary focalization occurs depends upon the following factors: (1) The lack of localized resistance due to deficient blood supply, trauma, and factors governing individual predisposition and localized sensitization; (2) the specific elective tissue affinity of bacteria.

There is no doubt but that the lack of resistance is an important factor in the occurrence of any infection. Exposure to cold, over-fatigue, and starvation have long been recognized as important factors predisposing to general infection. The lessened resistance accompanying these conditions probably depends upon circulatory and metabolic changes. In the mechanism of the focalization of infections in certain tissues as the result of metastasis through the blood-vascular system, a lack of localized resistance is also an apparent factor. The high incidence of infection in those organs undergoing a retrograde metamorphosis after childhood, such as the appendix and gall-bladder, may best be explained as being due to a deficient blood supply, because of the lack of functional activity. The predisposition to infection of periarticular structures, the tendinous portion of muscles, and the endocardium of the valve leaflets may also be explained on the basis of an intrinsically poor blood supply, as compared with the functional activity of these structures. It is probable that the important underlying factor in the blood supply of tissues is the amount of available oxygen present, since the bacteria of low virulence, but highly sensitive to oxygen, localize in those structures in which the blood supply, and therefore the oxygen and food requirements, are low. Since the bacteria belonging to the group of lower virulence have been shown to be the most common invaders this may explain the prevalence of infection of the structures just mentioned, not only on the ground of lessened resistance due to an anatomical defect but also on the ground of a specific elective affinity of the organisms for tissues of that type.

Trauma is an evident factor in lessened resistance, but it must be considered not alone from the standpoint of the destruction of anatomical integrity but from the standpoint of those chemical changes which disturb the zymotic action of the cells themselves. Circulatory changes due to disturbed function traumatize tissue and permit localization of infection. It has been suggested that such traumatism may best be explained on the basis of disturbed oxygen content in tissues.

Individual and family predisposition are factors in resistance. Experimental experience shows that lesions may be produced by the intravenous injection of a pathogenic microorganism in some animals, while it fails to produce any demonstrable reaction in others of the same

species. Our ignorance of the causes of such variations is concealed under the term "differences in vitality."

Local sensitization of tissues may be classified as a form of traumatism. Its relation to focalization is important. That sensitization of tissues to bacterial invasion plays an important rôle in specific localization was shown by Faber, who found that, either by repeated intravenous injections of streptococci of attenuated virulence or by the injection of killed streptococci into the joint cavity, he was able to sensitize the synovial membrane so that a subsequent intravenous injection of living streptococci of the same strain gave rise to a definite arthritis. The studies on foreign protein sensitization and anaphylaxis already referred to also suggest a general lowered resistance or hypersusceptibility. Localized sensitization probably occurs in a similar manner, as the result of previous infection in a given tissue or as the result of constant stimulation of such tissue by the endotoxins of the bacteria of specific pathogenicity confined either in the primary focus or in the tissues themselves. While these factors governing lessened resistance play an important rôle in bacterial invasion, the specific localization at a point distant from the primary focus apparently depends upon some special property of the bacteria themselves. *Bacteriemia* occurs at some time during the course of pneumonia and typhoid fever and yet in the former the usual localization is in the lung while in the latter the characteristic lesion is in the lymphoid follicles of the intestines. The isolation of streptococci from the blood in acute rheumatic fever is evidence of a generalized blood infection but the lesions are usually confined to the serous membranes alone. In a case exhibiting skin and glandular manifestations simulating syphilis, reported by Stengel, White and Evans, a streptococcus was isolated from the blood and from a tonsillar focus of infection, yet there were no other demonstrable lesions than those of the skin and the glands. These clinical illustrations strongly suggest the development of a specific elective affinity of bacteria for certain tissues under predisposing conditions.

That organisms may lose this specific tissue pathogenicity and still persist in the circulating blood (which is evidence that they are pathogenic invaders) without producing noticeable lesions, was noted in this case simulating syphilis following the subsidence of the skin and glandular manifestations and has been reported by others in cases in which the articular manifestations in rheumatic fever have disappeared. Such a *chronic bacteriemia* suggests that predisposing factors not only produce lessened local resistance but permit the organisms to develop certain specific characteristics as regards localization in tissues.

Specific Elective Tissue Affinity of Bacteria.—That bacteria develop a specific tissue affinity was established by the experiment of Forssner in 1902, when, by cultivating streptococci showing no specific pathogenicity for the kidney in kidney tissue and kidney extract he was able to demonstrate that such microorganisms develop special affinity for kidney tissue when injected intravenously into animals. When such organs were subsequently isolated from the kidney and grown upon artificial

media they soon lost this special affinity for the kidney. In 1906 Billings and Rosenow in studying chronic infectious endocarditis made observations which indicated that the elective affinity of the streptococcus-pneumococcus group was dependent upon the transmutability of the members of this group. The original cultures from the eleven cases of chronic infectious endocarditis were the *Streptococcus viridans* or *mitior* as described previously by Schottmüller. Owing to the low degree of virulence exhibited in animals by this organism, it was necessary to increase its virulence by various cultural methods and animal inoculation with successive strains, with the final result that there was developed an organism of high degree of virulence with the cultural and pathogenic characteristics of the pneumococcus. They reported their results as indicating that the pneumococcus was the etiologic factor in chronic infectious endocarditis. It is interesting to note the somewhat similar experience of Poynton and Paine in their studies on the etiology of rheumatic fever. These authors isolated the diplococcus from patients with rheumatic fever, this producing, when injected in rabbits, immediately after isolation, an acute non-suppurative arthritis and simple endocarditis, but, when injected after months of subculturing, producing a malignant endocarditis. From the simple endocarditis they were unable to regain the microorganism, while from the malignant endocarditis positive cultures were obtained. These authors concluded that the organism was not specific in its action, but that it could produce either simple or malignant endocarditis. Rosenow, however, concluded that, in his series of cases, he was dealing with the same organism which, because of cultural methods and animal passage, had changed its form, cultural characteristics, virulence, and specific pathogenicity for animals.

Transmutability of the Members of the Streptococcus-Pneumococcus Group.—In support of Rosenow's transmutation experiments, other observers have noted definite morphological and chemical reaction variations in given strains of streptococci and pneumococci after repeated culture and animal passage. Buerger and Rittenberg have observed that there are marked differences between the pneumococci isolated from the blood and those from the metastatic abscesses in puerperal sepsis. Rosenow has demonstrated similar variations in the same organism isolated (1) from the blood and (2) from a complicating otitis media in pneumonia. Anthony noted changes in the hemolyzing property of streptococci isolated from scarlet fever when grown on blood agar for a long time.

In order to classify the members of the group, Rosenow followed the nomenclature of Schottmüller, who described three types of the streptococcus isolated from man: the *Streptococcus viridans* (*mitior*), the *Streptococcus hemolyans* (*longus*), and the *Streptococcus mucosus* (*pyogenes*), each showing definite morphological, cultural, pathogenic and immunological differences. Haessli later confirmed this clinical differentiation of streptococci. Rosenow included the pneumococcus in this grouping. The diagram in Fig. 2 shows graphically the relation of the members of the streptococcus-pneumococcus group, based on the degree of virulence and sensitiveness to oxygen and on the variations

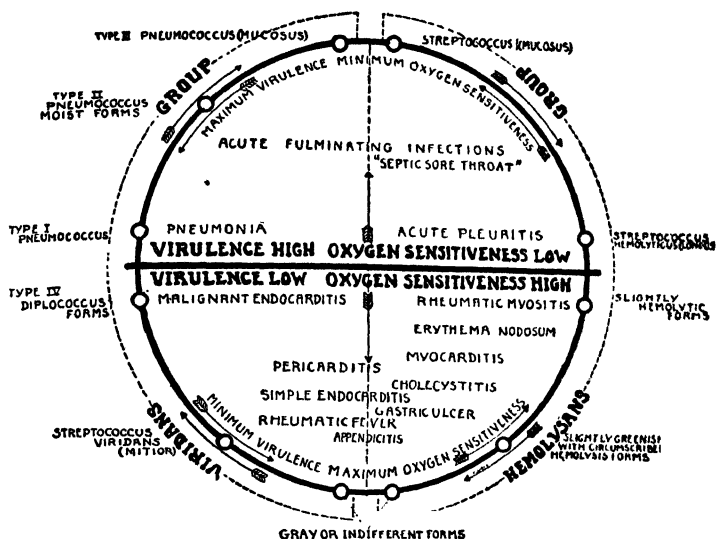


FIG. 2.—CHART SHOWING POSITION OF VARIOUS MEMBERS OF THE STREPTOCOCCUS PNEUMOCOCCUS GROUP AS REGARDS VIRULENCE, SENSITIVENESS TO OXYGEN, AND REACTION UPON BLOOD AGAR ON ISOLATION, AND THE PROBABLE POSITION AS REGARDS TRANSMUTATION OF FORMS BASED ON THE EXPERIMENTAL WORK OF ROSENOW.

The equatorial line separates the organisms according to degree of virulence and sensitiveness to oxygen. The polar line separates the organisms according to reaction on blood agar, the green-producing forms being on the left, the hemolyzing forms being on the right, the gray and indifferent forms occupying a position between the two groups. The arrows on the circumference indicate the changes in degree of virulence and oxygen-sensitiveness. Experimentally the following changes in form have been noted: "Retrospective" mutation: (a) From the *Pneumococcus mucosus*, at the upper left-hand side, down through the pneumococci group to the *Streptococcus viridans*, at the lower left-hand side (*in vitro*). (b) From the *Streptococcus hemolyticus* on the right-hand side down through the indifferent forms to the *Streptococcus viridans* on the lower left-hand side (*in vitro*). "Progressive mutation": (a) From the *Streptococcus viridans* through the pneumococci group to the *Pneumococcus mucosus* (by animal passage). (b) From the *Streptococcus hemolyticus* to the *Streptococcus mucosus* at the upper right hand side (by animal passage).

The position of the diseases within the circle indicates roughly the relation of these diseases to the underlying type of pathogenic organism designated by the small circle on the circumference. This grouping must not be taken to be more than a rough approximation. For example, the type of organism usually causing appendicitis is either the *Streptococcus viridans* or one producing a greenish discoloration with a slight zone of hemolysis around the colony. When the virulence of this organism is increased it tends to select the stomach or gall bladder upon which to focalize. On the other hand, while rheumatic fever is usually produced by the *Streptococcus viridans* or greenish forms with a slight zone of hemolysis around the colony, when the virulence of this form is increased it tends to develop the characteristics of the pneumococci type.

in morphology, cultural and immunological reactions. Experiments indicate that mutation depends upon variations in oxygen tension, in the tonicity of cultural media and on growth in symbiosis with other bacteria. Recently Oliver and Perkins have shown the effect of oxygen tension upon the cultural reactions of bacteria, and Wherry and Ervin its effect upon the growth of bacteria. By varying the amount of available oxygen and the tonicity of the media and by animal passage, changes were noted in a strain of *Streptococcus hemolyticus* to the *Streptococcus viridans* and to the pneumococcus. These changes in morphology and chemical reaction in this strain of streptococcus were associated with variations in the specific pathogenicity for animals, and led to the conclusion that the various lesions being produced by members of the streptococcus-pneumococcus group were due to mutation forms acquiring morphologic and biologic variations, according to the reaction of the tissue in which they grew, and a special elective affinity for tissues having a similar reaction. It would seem, therefore, that focalizations are no longer to be looked upon merely as a place of entrance of bacteria, but as a place where conditions are favorable for them to acquire the properties which give them a wide range of affinities for various structures. In the production of mutation forms, those that occur *in vitro* may be spoken of as "retrogressive" and those that occur as the result of animal passage as "progressive," because in the former the virulence, fermentative powers and other evidences of a vigorous life are diminished, whereas in the latter they are usually increased.

Laboratory Evidence of Elective Affinity of Bacteria.—Rosenow in his experiments selected strains of streptococci both from the characteristic lesions and from the suspected primary focus of infection in cases of appendicitis, gastric ulcer, cholecystitis, erythema nodosum, myositis and endocarditis; from the tonsils and spinal fluid in herpes zoster, and from the tonsils and Steno's duct in epidemic parotitis. The several strains from these sources were injected intravenously into rabbits and dogs and the following results were obtained: *

"Fourteen strains from appendicitis produced lesions in the appendix in 68 per cent. of the sixty-eight rabbits injected, which is in marked contrast to an average of only 5 per cent. of lesions in the appendix in the animals injected with the strains as isolated from sources other than appendicitis. Eighteen strains from ulcer of the stomach or duodenum produced hemorrhages in 60 per cent. and ulcer of the stomach or duodenum in 60 per cent., a combined total of 74 per cent. of the 103 animals injected, in contrast to an average of 20 per cent. hemorrhages and 9 per cent. ulcer following injection of other strains. Twelve strains from cholecystitis produced lesions in the gall-bladder in 80 per cent. of the forty-one animals injected in contrast to an average incidence of lesions here of only 11 per cent. with the other strains. Twenty-four strains from rheumatic fever produced arthritis in 66 per cent., endocarditis in 46 per cent., pericarditis in 27 per cent., and myocarditis in 44 per cent. of the seventy-one animals injected, in contrast to an average

* Rosenow, E. C. *Jour. of Amer. Med. Assn.*, 1915, lxx, 1687.

of arthritis in 27 per cent., endocardial lesions in 14 per cent., pericarditis in 2 per cent. and myocarditis in 10 per cent. of the animals injected with strains from sources other than rheumatic fever. Six strains from erythema nodosum produced lesions of the skin in 90 per cent. of twenty animals injected, in contrast to an average of 2 per cent. in the animals injected with the strains from sources other than erythema nodosum and herpes zoster. Eleven strains from herpes zoster produced herpetiform lesions of the skin, lips, tongue or conjunctivæ in 77 per cent. of the sixty animals injected, in contrast to the average of only 1 per cent. of what seemed to be herpes of the skin with other strains. Nine strains of streptococcal organisms from epidemic parotitis produced lesions in one or both parotid glands in 73 per cent. of the nineteen animals injected intravenously, in contrast to no instance of lesions here with the other strains. Three strains from cases of true myositis produced myositis in 75 per cent. and myocarditis (chiefly of the right ventricle) in 35 per cent. of the forty animals injected, in contrast to an average of myositis of 12 per cent. and myocarditis of 10 per cent. following injection of strains from sources other than myositis or rheumatic fever; and eight strains of *Streptococcus viridans* from chronic septic endocarditis produced lesions in the endocardium in 84 per cent. of the forty-four animals injected, in contrast to an average of 15 per cent. with the strains other than those from endocarditis.

"While the incidence of lesions in the organs following injection of the strains isolated from such organs is high, as shown by these figures, the appearances at the necropsy are even more significant. In many instances in which the animals survive the injection for some time, no other focal lesions could be found except those in the organ in question; and when the animal died early, these lesions were the marked feature and the associated ones were relatively insignificant. Frequently the injection of a very small dose was sufficient to prove the elective localization. This elective property was shown not only by the cultures from tissues and foci but also by the bacteria contained in the foci, directly injected in other animals.

"In many cases of both acute and chronic diseases the apparent atrium of infection was found to harbor streptococci having elective affinity; in the former usually only at the time of the attack, in the latter in some instances for months. The elective affinity, however, was less marked in the strains isolated from the supposed focus than in the strains isolated from the lesions in the various organs.

"The localization of the strains from appendicitis, ulcer of the stomach and cholecystitis as isolated, after cultivation and after animal passage, is of particular interest. These strains resemble one another very closely indeed in cultural and other respects. Those from appendicitis are the least virulent, those from ulcer occupy a middle position and those from cholecystitis are the most virulent. The virulence seems to be one of the factors that determines their place of survival after intravenous injection. Now if the localization is dependent to a certain extent on virulence, then the occurrence of ulcer and cholecystitis should

become greater as the strains from the appendix are passed through animals, and appendicitis should occur oftener after the strains from ulcer and cholecystitis lose virulence from cultivation on artificial media. This was found actually to be the case. In this connection other facts should be mentioned. None of the strains from appendicitis produced pancreatitis. The strains from ulcer and cholecystitis as isolated (mostly those from acute cases) produced pancreatitis in 3 per cent. and 5 per cent. respectively, of the animals injected. After animal passage, pancreatitis occurred in 15 and 19 per cent. respectively, while after cultivation on artificial media pancreatitis in no case was obtained. Lesions in the skeletal muscles occurred in 75 per cent. of the animals injected. The number of lesions in the muscles and myocardium in the animals injected with strains from myositis was often in proportion to the quantity injected, and occurred mostly in the tendinous portion and in the right ventricle.

"Lesions in the kidney were especially common after injections of streptococci from rheumatic fever (39 per cent.) and from endocarditis (20 per cent.). These occurred chiefly in the medullary portion in the former and in the glomeruli in the latter.

"Lesions in the lung, consisting usually of hemorrhages and edema, were rare following injection of the strains when isolated and after they were cultivated they occurred oftener after the virulence was increased by animal passage.

"That the streptococci are the underlying cause of the diseases from the lesions of which they were isolated is indicated further by the fact that they have elective affinity for the corresponding structures in animals. Moreover, the fact that the same streptococcus may be made to localize in different organs is in consonance with the knowledge that streptococci may cause diseases with different symptomatology. The possibility, however, that they are secondary invaders to some ultra-microscopic, filterable organism has to be considered. Filtrates of the streptococcal cultures from various diseases were injected intravenously. In some instances the filtrates produced lesions in the organs from which the strains were isolated; the lesions, however, were not due to living organisms because the broth which was inoculated and incubated with the tissues failed to produce any lesions. The results, while inconclusive, may be said to indicate that streptococci produce substances which cause injury specifically in the tissues from which the strains are isolated."

From these experiments and later ones directed more particularly toward the determination of an elective affinity of bacteria for nervous tissue. Rosenow suggests that the frequency of localization of bacteria in structures about joints, the more tendinous portion of muscles, the endocardium, the ciliary body, the iris and the limbus may be due to the fact that there is a gradation from an abundant to a very scanty blood supply in these structures and hence a gradation of the supply of available oxygen, thus inviting localization by affording opportunity for optimum growth of bacteria.

COMMON SITES OF ETIOLOGIC FOCAL INFECTIONS

Focal Infections of the Nasal Tract.—A high incidence of bacterial invasion through the mucosa of the nose and the nasopharynx has already been pointed out. It is probable that the incidence of persistent focalized infections in that tract is much greater than the literature indicates. All of the factors predisposing to bacterial invasion exist in the upper respiratory tract, but the difficulty in diagnosing persistent infections in this region, especially of the non-suppurative variety, has led many specialists to consider their incidence much less than the tonsillar and dental infections. One has only to consider the anatomy of the nasal cavity and its accessory sinuses (see Fig. 3) and the general prevalence of acute nasal infections, to be impressed with the probability of the more or less common occurrence of nasal focalization.

The extension of an acute inflammatory process into the accessory cells of the nose is the common occurrence in those nasal infections associated with systemic symptoms loosely called "grippe." Unfortunately, the natural drainage from the accessory sinuses is defective. The subsidence of the superficial nasal infection is frequently not accompanied by a similar subsidence within the accessory cells. Swelling of the mucous membrane of the nose due to circulatory disturbances may completely obstruct natural drainage from the air-cells. Where there is an acute suppurative process the evidence of a pent-up infection producing local and systemic reaction is evident. More frequently the non-suppurative infections exist and with the obstruction of natural drainage the air-cell is placed under pressure which produces circulatory disturbances predisposing to chronic focalization beneath the non-resistant mucous membrane of the cells. It therefore must be borne in mind that nasal foci of infection are much more frequent than the usual methods of clinical examination indicate. In the author's series of cases of chronic arthritis, a definite nasal infection was found in 60 per cent. of the cases. Crowe points to the prevalence of nasal foci of infection associated with tonsillar infection.

The probability of persistent sinus infection associated with only indefinite local symptoms (predisposition to nasal infection, recurring headaches, nasal catarrh) was illustrated in a case that came under the author's observation in 1911. The patient had had severe influenza in 1893, at a time when there was a widespread epidemic due to the *Bacillus influenzae*. Since that time outside of Boston and New York there had been only sporadic cases of true influenza. In 1911 the patient developed an atypical pneumonia associated with hypoleukocytosis. The sputum contained as the predominant microorganism the *Bacillus influenzae* and the same organism was isolated from a mucoid secretion wiped out of the middle meatus in the ethmoid region. With the radical correction of this persistent ethmoiditis the patient's predisposition to frequent nasal infection was overcome.

Nasopharyngeal infection is common in children in the form of infected lymphoid tissue, *adenoids*. Primary tuberculosis of the adenoids

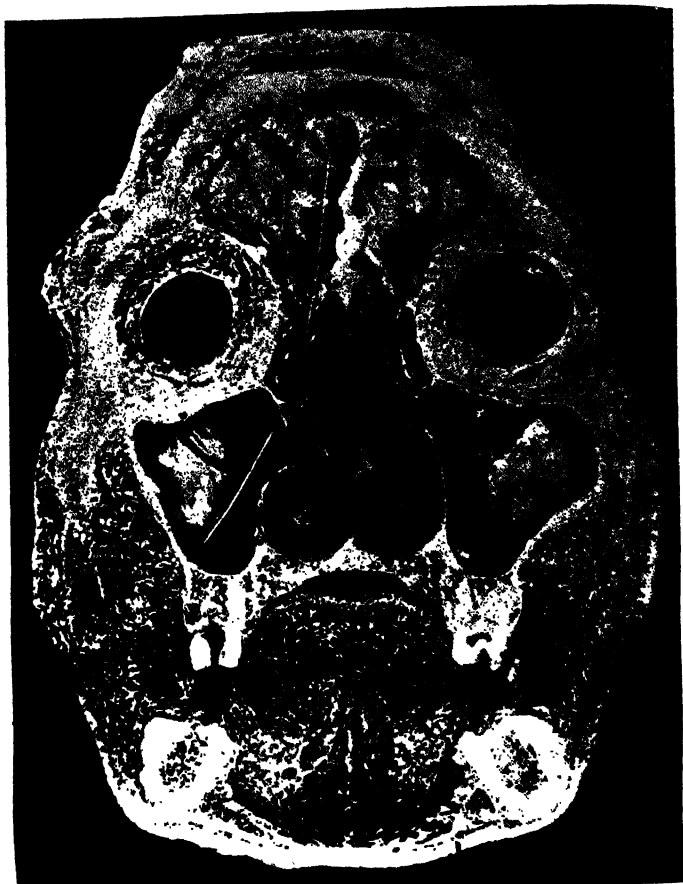


FIG. 3.—VERTICAL TRANSVERSE SECTION OF HEAD CUT IN THE REGION OF THE MOLAR TEETH, SHOWING RELATION OF NASAL CAVITY AND ITS ACCESSORY SINUSES.

The section exposes the frontal, ethmoidal and maxillary sinuses. The wire passes from the frontal sinus downward through the infundibulum, the hiatus semilunaris and the ostium maxillare into the maxillary sinus. The poor, natural drainage of these cells is well shown and explains the persistent character of an infection when once the sinus is invaded. The close proximity of the dental structures to the floor of the maxillary sinus explains the frequency of interrelated infection in these two regions. (After M. H. Cryer, "The Internal Anatomy of the Face." Lea and Febiger.)

was found in 14 out of 100 cases by Crowe, who also states that at least 25 per cent. of children with adenoids have definite indication for their removal, the most common being otitis media. Even after removal of the large infected masses infected lymphoid tissue may persist. Sphenoid infection is commonly associated with adenoids and may persist through adult life.

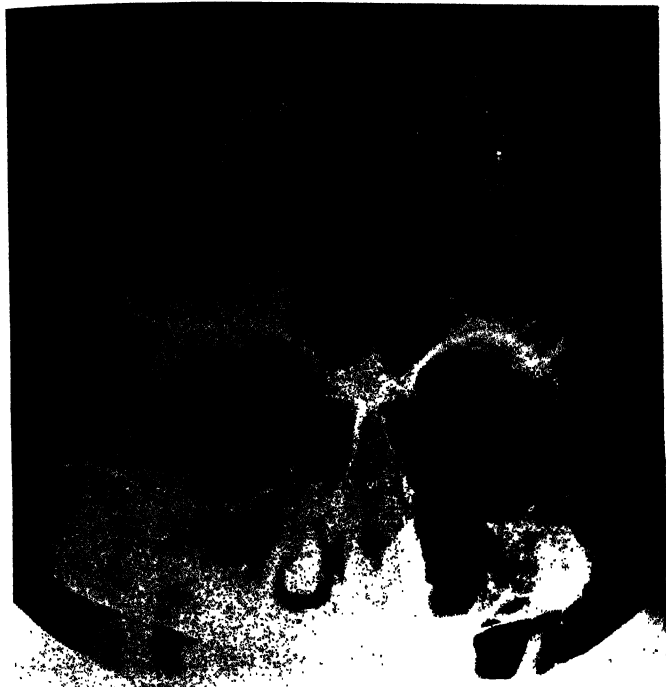


FIG. 4.—ROENTGENOGRAM OF A CHRONIC MAXILLARY SINUSITIS, SHOWING THE ANTRUM FILLED WITH GRANULATION TISSUE.

From a case of chronic infectious arthritis which improved rapidly following intranasal drainage and treatment.

The etiologic relation of nasal foci of infection to acute and chronic, localized or general, systemic diseases is firmly established. In our own observation on young adult morbidity the incidence of the etiologic nasal focus in acute systemic manifestations is the highest. In later life and in the more chronic forms of secondary manifestations the relative incidence is lower. However, in bronchial asthma, in the recurring headaches of the migraine type, or as described by Patrick the "indurative or

rheumatic" type, in recurring or chronically progressive eye infections, in chronic myositis and in certain cases of chronic arthritis, we have found a chronic sinus focal infection to be a common etiologic factor. The relations of diphtheroid infections of the nasal tract have been noted in Hodgkins' disease by Bunting and Yates.

The types of organisms usually isolated from nasal focal infections are the members of the streptococcus-pneumococcus group, the diphtheroid organisms, the *Bacillus influenzae*, the *Micrococcus catarrhalis*, and the staphylococcus.

Tonsillar Foci of Infection.—Bacterial invasion of the tonsils and the lymphoid tissue of the nasopharynx is almost universal during childhood. Acute systemic diseases secondary to acute infection of the tonsils

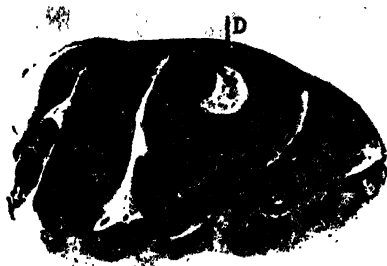


FIG. 5.—SECTION OF A TONSIL WHICH CLINICALLY APPEARED TO BE HEALTHY, SHOWING A SMALL ABSCESS (D).

From a case of subacute infectious arthritis, Tonsillectomy was followed by rapid subsidence of the joint infection. The cross-section of the crypts also illustrates the natural poor drainage of the tonsil, which predisposes to bacterial invasion and focalization. (Magnified $\times 8$.)

and adenoid tissue are common and generally recognized. There is no doubt that during the preadolescent period this lymphoid tissue plays an important rôle in the resistance against general bacterial invasion and therefore is more or less constantly subjected to primary invasion. The anatomical structure of the tonsil is such that retention of infection is predisposed because of imperfect drainage.

Invasion beyond the basal membrane of the tonsillar crypts is frequent and circumscribed areas of latent infection occur. During young adult life, acute bacterial invasion of the tonsils, though not as frequent as that in the nasal cavities, occurred in 22 per cent. of our series of cases. This lessened incidence is probably due to repeated acute invasion during childhood, for of 5,735 students examined at the University of Wisconsin (Van Valzah) 42 per cent. showed macroscopic evidence of abnormalities of the tonsils. Many tonsils appearing innocent (see Fig. 5), however, may be diseased, so that the percentage of tonsillar

infection mentioned above does not indicate the actual frequency of tonsillar invasion. Furthermore, patients showing evidence of a complete tonsillectomy were not included with those classed as having diseased tonsils.

Tonsillar stumps which are atrophied and scarred tonsils are particularly apt to be the seats of chronic infection. Hypertrophied pharyngeal lymphoid nodes are often infected, especially when persisting through adult life. The so-called "lingual" tonsil is a favorite site for persistent infection.

The infecting agents occurring in the tonsillar foci are mainly of the streptococcus-pneumococcus group. In the acute invasion seen in the various milk-borne epidemics, the infecting agent belonged to the streptococcus-pneumococcus group. In the acute exanthemata Tunncliffe has determined definite differences in the streptococci in smears from the throats in measles, rubella and scarlet fever. In measles the smears showed many small round diplococci; in rubella elongated pointed cocci in pairs, sometimes in chains, often showing a narrow capsule; in scarlet fever cocci, usually round, in pairs or chains of rarely more than four, with generally a wide capsule (*Streptococcus hemolyticus*). In measles and rubella similar cocci were isolated from the blood. The *Streptococcus hemolyticus*, while a frequent acute invader, may persist in a modified form in a chronic tonsillar focus. In epidemic anterior poliomyelitis, Rosenow finds a *pleomorphic* streptococcus invading the tonsil. The relatively non-virulent *Streptococcus viridans* is normally found on the surface of the tonsil and is probably the most frequent invader of the tonsillar mucous membrane, lying dormant until conditions are ripe for its secondary invasion and localization. The *Micrococcus catarrhalis*, the *Bacillus influenzae*, the diphtheroid organisms and the *Bacillus tuberculosis* are frequent invaders of the tonsillar tissue. Crowe emphasizes tuberculosis of the tonsils as a focal point from which secondary tuberculous infection may occur.

Smith, Middleton and Barrett found the *Entameba gingivalis* in the tonsils of five out of seventeen patients examined. Evans, Middleton and Smith found the entamebæ in 97 per cent. of the goiter patients with diseased tonsils. As in dental infections the entamebæ probably play a symbiotic rôle in the primary and secondary invasion of pathogenic microorganisms.

Billings, in his studies on chronic infectious arthritis, found infections of the tonsils the most frequent etiologic focus. The etiologic relation of tonsillar infection to the acute and chronic inflammations is suggested by the fact that many of these conditions are due to the *Streptococcus viridans*, a type of organism which is almost always present on the tonsillar mucous membrane and which consequently is apt to invade and focalize at that point.

Aural Focal Infections.—Infection of the middle ear by extension through the Eustachian tube is considered a frequent occurrence, but the infection may also take place as an hematogenous metastasis. The metastatic complications of otitis media are not uncommon and usually

involve the venous sinuses and meninges. Mastoiditis, secondary to such an infection or due to hematogenous invasion from tonsillar or nasal foci, is frequent, especially in children. Acute mastoiditis may give rise to general bacteriemia with multiple acute lesions, or sinus thrombosis or meningitis. Chronic otitis media and chronic mastoiditis must always be looked upon as sites of focal infection in relation to secondary local or systemic infections. The lymphatic drainage of these regions is usually involved, a secondary lymphadenitis resulting. The bacteria usually isolated belong to the streptococcus-pneumococcus group, though either the staphylococcus, the *Bacillus influenzae* or the diphtheroid organisms may be the predominant infecting agents.

Oral Focal Infections.—DENTAL AND ALVEOLAR TISSUES.—The frequency of bacterial invasion and focalization in the dental and peridental tissues, and the relation of such infection to local and systemic diseases, has been clearly established by clinical observations and animal experimentation. The frequency depends mainly upon the age period of life. It is most common in the adult and less prevalent in the young. Moorehead states that the period of greatest danger from mouth infections is from twenty-five to sixty years of age. The same author found that the incidence of chronic mouth lesions in a group of over 700 carefully analyzed cases showed percentages ranging from 69 to 80 per cent. according to the age period. Irons, in the analysis of a series of 329 cases exhibiting varying types of systemic diseases secondary to foci of infection, found that the incidence of alveolar abscess was preponderant over other localized infections, ranging from 23 per cent. to 76 per cent., being highest in the arthritis group, a disease of middle life. In a study of 50 cases of chronic arthritis, the author demonstrated an etiologic dental focus in 70 per cent. of the individuals, all of whom were well advanced in years. Ulrich, as the result of the examination of 1,350 dead teeth, found 83 per cent. of them with apical abscesses. Of those artificially devitalized, 68 per cent. had similar lesions. Langstroth found, in 30 cases of gastric or duodenal ulcer, that 44 per cent. showed definite alveolar abscesses. Irons, Brown and Wadler found dental foci in 18 per cent. of iritis cases and that it was the only demonstrable focus in 7 per cent. of the individuals. This relative incidence indicates, therefore, that in the more chronic systemic infections of middle life the prevalence of dental foci is high, while in the more acute conditions of early life it is low.

Dental foci may exist either as a periapical abscess, a pericementitis, a pulpitis, a granuloma or an interstitial gingivitis, both suppurative (Riggs' disease) and non-suppurative. The infecting agent is usually a streptococcus belonging to the low-virulence group, the *Streptococcus viridans*. Gilmer and Moody, in a bacteriologic study of alveolar abscesses and infected root canals, found the streptococcus to be the predominating organism and in a later communication classified the organism as a *Streptococcus viridans*. Hartzell reported 220 cases in which he isolated the *Streptococcus viridans*, not only from confined dental abscesses, but from the superficial tissues of the peridental membrane.

The type of streptococcus depends upon its degree of virulence and as the vast majority of persistent dental infections are of low virulence, producing slow and chronic forms of secondary manifestations, the type usually found is the *Streptococcus viridans*. At times, however, such foci have a high degree of virulence, producing sudden and acute manifestations, the streptococcus possessing mild hemolytic properties.

There is abundant clinical evidence to establish definitely the etiologic relation of dental infections to systemic diseases. Goadby, in 1912, reported three cases of arthritis deformans in which correction of the dental infection was followed by a subsidence of symptoms. Since that time other observers* have emphasized dental foci as the source from which disease-producing bacteria are disseminated throughout the body. Keyes' observations are especially interesting from the standpoint of the relation of dental foci of infection to body resistance against general infections. With the establishment of dental prophylaxis among children in an orphan asylum, the percentage of infectious diseases was reduced 59 per cent. at the end of six months and to approximately 2 per cent. during the following year.

Experimentally, Rosenow reports that the immediate intravenous injection of streptococci isolated from dental foci may produce in animals lesions similar to those existing in the patient from whom the organism was obtained. Moody reports similar results. Hartzell and Henriei were able to produce lesions in the heart, aorta, muscles, joints and kidney of animals, but were unable to demonstrate a definite elective affinity on the part of such organisms.

In 1914, Barrett and Smith, Bass and Johns described the relation of the *Entameba gingivalis* to pyorrhea alveolaris. These observations leave little doubt but that the entamebæ play an important rôle in the production of the destructive changes in pyorrhea and probably exert a symbiotic rôle in the bacterial invasion and the systemic symptoms produced by the bacterial toxins. Evans and Middleton, in a preliminary report, noted the effect of the removal of the entamebic infection upon the subjective and objective symptoms of patients with oral entamebiasis complicating dental infections. While the bacteria undoubtedly play the specific rôle in the production of secondary lesions, attention should be given the entamebæ as a factor in certain secondary manifestations.

SALIVARY GLANDS.—Direct extension of bacteria along the ducts of the salivary glands is frequent, thereby permitting primary bacterial invasion into the gland. There is evidence, however, that hematogenous infection of the gland from other foci occurs much more frequently than formerly believed. Persistence of the infection in the gland, whether due to primary invasion or secondary metastasis, acts as a primary focus from which secondary infections and systemic reactions may arise. The type of organism usually found in such infections belongs to the streptococcus-pneumococcus group, though invasion by other bacteria frequently occurs.

Lymph-node Focal Infection.—Acute infections of the nose, naso-

* Eisen; M. H. Fischer; Ivy; Mayo; Preble; Potter; White.

pharynx, tonsils, middle ear or mastoid are frequently accompanied by an invasion of the lymphatics draining those areas. Following the subsidence of the primary acute infections, the lymph glandular infection often persists near the *portal of entry*; similar lymphatic involvement and similar persistence of infection may occur in the lymphatic drainage of any region of secondary infection.. It is important to bear this in mind, both from the diagnostic and prognostic standpoints, for large lymph-nodes indicate an infection in the areas they drain and may continue as persistent foci of infection even after the primary focus has been removed. But the lymphatic infection may disappear following the removal of the primary focus. The prevalence of persistent lymphatic involvement, however, is shown in the statistics of Kretz, who, in 600 autopsies, found that in 90 per cent. of the bodies examined the cervical glands were infected with the streptococcus, while 10 per cent. showed the presence of other bacteria. Lasser, in the examination of 1,216 patients, found that 89.5 per cent. had palpably enlarged glands. In children the superficial glands of the anterior triangle were involved, while the deeper glands at the angle of the jaws along the internal jugular vein were infected in adults. Kretz points out that the so-called glandular fever in children is an evidence of acute focalization in the lymphatics which may arise as direct invasion of the lymph-vascular system or secondary to hematogenous infection. Chronic lymphatic infection is apt to produce systemic disturbance whenever the areas which the lymphatics drain are the seats of acute infection. This explains the common clinical experience of the recurrence of acute systemic manifestations following the radical removal of primary foci of infection. W. J. Mayo, in a recent article, emphasizes the importance of the etiologic relation of glandular foci as the cause of tuberculous peritonitis.

Pulmonary Focal Infection.—Focalization in the respiratory tract is common. Repeated bronchial infection, in which the peribronchial lymph-nodes are involved, leads to chronic focalization in the bronchial submucosa and in the peribronchial glands. Small bronchiectatic cavities are found to be much more frequent than was previously supposed since roentgenography has assisted us in pulmonary diagnosis. Such cavities must be looked upon as possible etiologic foci of infection. Chronic fibroid lesions are found especially in the roentgenograms of those individuals giving the history of the acute exanthematous diseases. In such cases, the existence of previous infection is indicated by the secondary fibroid changes at the hilum of the lung and in the lymphatic tree of the bronchus to the lower lobe.

The anatomical structure of the lung, however, does not predispose to pent-up infection and, while such infection is prevalent, secondary manifestations from such foci are not so common. It is true, however, that such foci sometimes produce those systemic disturbances that lead to the diagnosis of incipient tuberculosis. While it is better to err on the safe side in the diagnosis of tuberculosis, yet it must be borne in mind that chronic pyogenic infections in the pulmonary tract may

produce chloro-anemia, intermittent fever, neurasthenia, and those metabolic disturbances associated with tuberculous infection. The types of bacteria found in the foci of the bronchial tract are the same as those found in the upper respiratory and upper digestive tracts.

Etiologic Foci of Infection in the Gastro-intestinal Tract.—**GALL-BLADDER.**—The gall-bladder is one of the sites of predilection for the secondary focalization of bacteria which invade the blood stream from a portal of entry or from a primary focus of infection. Chronic cholecystitis is usually of streptococcic origin, although the *Bacillus typhosus* may be a primary factor in the bacterial invasion. The demonstration of streptococci in the walls of gall-bladders and in the centers of gall-stones is sufficient evidence that in many cases of cholecystitis and cholelithiasis this region must be looked upon as a probable point of focalization producing secondary systemic symptoms. It must be borne in mind, however, that the growth of organisms in gall-bladder tissue does not develop an especial affinity for any other tissue in the body unless the virulence of the organisms is increased or decreased. Experiments indicate that when the former occurs pancreatic infection may be associated with a cholecystitis; when the latter occurs gastric ulcer and appendicitis may result.

Tuberculous foci in the gall-bladder, either secondary to lymphatic invasion or to hematogenous metastasis, is sometimes an etiologic factor in tuberculous peritonitis, as pointed out by W. J. Mayo. The type of organisms isolated from the gall-bladder foci of infection belong mainly either to the typhoid-colon groups, the streptococcus-pneumococcus group or the *Bacillus tuberculosis*.

APPENDIX.—The appendix is involved in the same way as the gall-bladder and may act as a latent focus of infection producing systemic disturbances. The prevalence of appendicitis indicates the importance of this locality as the site of a probably persistent focal infection producing a local or systemic disease. The frequent failure to relieve systemic symptoms by the removal of a chronically diseased appendix is often due to the persistence of a primary focus of infection in the nose or throat from which the secondary localization in the appendix occurred. The etiologic relation of persistent infection of the appendix to gastric ulcer is recognized clinically and has been proved experimentally. W. J. Mayo speaks of the appendix as a relatively infrequent site of a tuberculous focus producing tuberculous peritonitis, while Eisendrath emphasizes the frequency of this etiologic relation.

INTESTINAL TRACT.—The *intestines* are similarly infected either as the result of hematogenous metastases from nasal or throat infections or by direct invasion of pathogenic microorganisms through the intestinal mucosa. In 1899, Adami pointed out the more or less constant invasion of pathogenic and non-pathogenic bacteria through the intestinal wall of animals with lodgment in the mesentery glands or in the tissues far distant. Nicholls showed that in rabbits in apparent health the mesenteric glands contain abundant bacteria. Herter, in explaining the relation of intestinal infections to systemic disturbances, also em-

phasizes the invasive property of bacteria toward the intestinal mucosa, dependent both upon the type of organism and upon the cellular resistance of the mucosa. It is this bacterial invasion through the gastro-intestinal tract that may lead to the systemic disturbances attributed to so-called "auto-intoxication," a term universally used but improperly understood. "Auto-intoxication" should be applied only to those disturbances dependent upon abnormal alterations in the hormones and upon the improper elimination of the products of catabolism, autolysis, and impaired metabolism. Intestinal stasis due to spastic constipation, to such congenital defects as redundant colon, veils and membranes, and to inflammatory adhesions, predisposes to bacterial invasion and the absorption of toxins. In so far as bacterial invasion, or the absorption of the bacterial endotoxins or of those toxins produced by abnormal bacterial fermentation of the intestinal contents, brings about the types of disturbed metabolism mentioned, intestinal stasis may be said to produce "auto-intoxication." It is the bacterial invasion, however, producing what Adami terms "subinfection," that is the usual cause of the various systemic reactions rather than the effect of the products of putrefactive changes in the intestinal contents.

Infections of the *rectum* and *sigmoid* may occur as the result of primary invasion and focalization or as the result of hematogenous invasion. Persistent foci of infection in this region may produce both local and systemic reaction. Soper reports 50 cases in which there existed pyogenic infections of the mucosa of the rectum and sigmoid with resulting systemic effects. In 23 of these cases, ranging from twenty-one to forty-nine years of age, he noted symptoms usually ascribed to auto-intoxication and neurasthenia; in 12 migraine and spastic constipation were the predominating symptoms; in 10 cases metastasis occurred, causing either appendicitis, cholecystitis, gastric and duodenal ulcer, or kidney disease. In this group of cases there was a tendency to rectal hemorrhage. In 7 cases nephritis and arthritis deformans were the principal conditions noted. Beveridge also reports upon the apparent etiologic relation of gastro-intestinal infection to arthritis. In those cases of dysentery from which he was able to isolate micrococci there was an associated arthritis. In those cases free from joint manifestations, the cultures were negative. Infected hemorrhoidal thrombi frequently produce such acute manifestations as hepatic abscess and septicemia.

The members of the streptococcus-pneumococcus and the typhoid-colon groups are the common forms encountered in focal infections of the gastro-intestinal tract, while the *Bacillus tuberculosis* and the dysentery forms are frequent invaders. Any pathogenic organism, however, may focalize in this tract.

Etiologic Foci of Infection in the Genito-urinary Tract.—Direct bacterial invasion, followed either by acute secondary manifestations or by primary focalization, may occur at any point along the genito-urinary tract. Hematogenous invasion from other foci is relatively frequent in the deeper structures of this tract. The vagina and uterus,

especially immediately after childbirth, are most frequently subjected to primary invasion. The fallopian tubes, the ovaries, the prostate and the seminal vesicles may be invaded by an ascending infection along the tracts but frequently are secondary to metastases. The author has studied one case in which metastatic abscesses occurred in the kidney and the testicles, due to the pneumococcus, three days after the crisis in a lobar pneumonia.

The urinary tract, the bladder, the ureter, and pelvis of the kidney may become infected secondary to the urethra, but the infection of the pelvis of the kidney is almost always a hematogenous invasion. Especially in children does an infection of the pelvis of the kidney occur secondary to an acute infectious disease or acute inflammation of the nose and throat, and must always be considered as a probable focus of infection producing systemic manifestation in the form of unexplained febrile reaction and toxic disturbances.

The endometrium is normally sterile even during an uncomplicated puerperium, as shown by Nicholson and Evans, but when once infected, either by the accidents of childbirth or by an ascending infection in gonorrheal vaginitis, it is apt to remain as a focalized infection capable of producing widespread secondary manifestations. Glandular, arthritic and general systemic manifestations are frequently caused by chronic endometritis. Infection of the fallopian tubes may be either gonorrheal or due to other coccal invasion when secondary to ascending infection, but it is much more frequently secondary to nasal and throat streptococcal infections than once believed. W. J. Mayo emphasizes the very important etiologic relation of tuberculous infection of the fallopian tubes to tuberculous peritonitis. The factors involved in the localization of infecting agents in the fallopian tubes apply to similar invasion and localization in the ovary.

Prostatic infection and seminal vesiculitis are frequent sources of infection and are most commonly gonorrheal in origin, but may be due to the streptococci and frequently to the *Bacillus tuberculosis*. Culver concludes that anaërobic as well as aerobic organisms may be the exciting cause of chronic prostatitis and spermatoecystitis, and that chronic infections of the prostate and seminal vesicles may be responsible for subacute and chronic arthritis. Other authors (Barney, Fuller, Young) have also noted that many arthritic cases have been cured, improved, or made non-progressive by draining a genito-urinary focus of infection.

In the bladder infections the colon bacillus may become highly pathogenic, due to increased invasive properties of that microorganism developed as the result of a mixed infection.

The following bacteria have been determined as producing focal infections in the genito-urinary tract: the gonococcus, the streptococcus-pneumococcus group, the staphylococcus, the *Bacillus tuberculosis*, the *Bacillus coli communis*, the *Bacillus typhosus*, the *Bacillus pyocyaneus* and the various diphtheroid forms.

Skin Focal Infections.—Any localization in the skin may become

the primary source of systemic infection, but, because of its easy detection and usually easy correction, the incidence of secondary manifestations resulting from such infections is low. The systemic infections secondary to widespread furunculosis and carbunculosis are not infrequent. Severe pustular acne is usually associated with toxic manifestations, as anemia and neurasthenia, and to a predisposition to various acute infections. Billings reports two cases of arthritis secondary to persistent foci of infection about the nails. Fischer reports a case of metastasis from an infected finger to the kidney producing perinephritic abscess.

ACUTE AND CHRONIC DISEASES SECONDARY TO FOCAL INFECTIONS

Acute and chronic manifestations that may arise secondary to focal infections may be either an acute or chronic inflammation produced by bacterial invasion into the various tissues or a disturbance of certain functions due to the effect of the bacterial endotoxins. These diseases are described fully from the standpoint of symptomatology, diagnosis, treatment, etiology and pathology under the various system headings.

Theoretically, any infectious process in the body may be the result of the hematogenous or lymphogenous invasion of bacteria that have been confined in the body by the defensive mechanism. Present experimental proof, however, is definite in only certain diseases.

The evidence of a probable elective tissue affinity on the part of the streptococcus-pneumococcus group suggests at least that a similar varying specific pathogenicity may be a property of certain other micro-organisms. No matter what the etiologic bacterium may be in a given lesion, the mechanism of secondary infection is probably the same.

In presenting the clinical and experimental evidence which has established the etiologic relation between focal infections and the disease to be discussed, it is not the intention to convey the impression that these diseases have no other etiology than that described. It is desired, however, to impress clinicians with the importance of considering the primary etiology of any disease of bacterial origin of the same importance as the symptomatology and the end pathology of that disease. It is also desired to point out the possible ultimate results of neglected, apparently benign localized infection, in order to show the necessity of treatment even in the absence of signs and symptoms of body reaction.

The laboratory experiments already described suggest variations in the strains of the members of the streptococcus-pneumococcus group with relation to: (1) structures lined by endothelium; (2) structures covered by epithelium; (3) eye; (4) thyroid; (5) pancreas; (6) kidney; (7) nerve tissue; (8) muscle tissue; (9) bone. Such an anatomical classification, however, does not imply that a particular strain of the streptococcus-pneumococcus organisms showing a special affinity for a

given tissue in one of the groups must necessarily show an election for all the other tissues in that group or that such an affinity is confined alone to the single group. The results of the animal experiments do show, however, a tendency on the part of bacteria to produce associated lesions in structures both within and without the anatomical groupings dependent upon the virulence of the organisms and apparently upon the oxygen tension in the tissues, such associated lesions resembling closely those observed clinically. As shown in Fig. 2, the same type of organism is found in cholecystitis, gastric ulcer and appendicitis, in the order of lessened virulence. The association of these diseases is a common clinical observation. The common occurrence of a persistent low grade infection of the appendix associated with acute gastric ulcer has led many observers to suggest that the latter was caused by the former, without clearly understanding the etiologic relation. The organisms focalized in the appendix may obtain that degree of virulence necessary to a special affinity for the stomach tissue. The same is true in regard to the secondary manifestation of cholecystitis in patients suffering with an appendiceal infection. Similarly, the organisms producing experimental acute non-suppurative arthritis and endocarditis are of the same type and again these are the manifestations observed clinically in rheumatic fever.

From experimental evidence and from clinical observation, it is seen that the possible immediate effects of invasion of the blood-vascular system by bacteria from a primary focus of infection may be either: (1) a "fulminating infection" in the form of a bacteriemia with multiple localized infections, due both to the high degree of virulence of the organisms and the general lack of resistance of the tissues against the infection; or (2) metastases to special tissues, dependent upon the factors governing the dissemination and secondary localization of bacteria, producing acute local inflammatory reaction.

Both the clinical and laboratory evidence at hand is sufficiently definite to permit the consideration of the following *acute localized infectious processes* as being due to hematogenous metastasis from a primary focalized infection:

Acute endocarditis
Acute pericarditis
Acute pleuritis
Acute peritonitis
Acute infectious arthritis
Acute tenovaginitis
Acute bursitis
Erythema nodosum
Purpura hemorrhagica
Acute bronchopneumonia
Acute cholecystitis
Acute appendicitis
Acute enteritis

Acute colitis
Acute gastric and duodenal ulcer
Acute conjunctivitis
Acute keratitis
Acute iritis
Acute iridocyclitis
Acute uveitis
Acute episcleritis
Acute choroiditis
Acute retinitis
Acute optic neuritis
Acute thyroiditis

Acute pancreatitis
Acute nephritis
Acute pyelitis
Acute neuritis
Acute myelitis
Acute poliomyelitis

Acute meningitis
Herpes zoster
Acute chorea
Acute myositis
Acute myocarditis
Acute osteomyelitis

The possible *remote* effects of persistent focalized infections are not so easily recognized. Chronic inflammations secondary to the acute manifestations just mentioned may be the result of localized infection in the tissues or due to continued or recurrent metastases from the primary focus. The most common and the most difficult to recognize in their etiologic relation to a chronic focus of infection are those conditions which arise as the result of persistent feeding from a focus of infection of an organism of such low virulence that symptoms of tissue reactions are lacking, the primary evidence of the diseased conditions being the result of disturbed function, either local or general.

Insidious and persistent bacterial focal infections have been found to bear an etiologic relation to hematogenous and lymphogenous production of the following *chronic inflammations*: chronic infectious arthritis, chronic bursitis, chronic endocarditis, chronic myositis, chronic neuritis, chronic colitis, chronic cholecystitis, chronic appendicitis, chronic gastric and duodenal ulcer, chronic nephritis. The endotoxins elaborated in and absorbed from such confined areas of infection appear to play an important rôle in the production of anemia of the various recurrent and chronic reactions of the anaphylactic type and of those manifestations which are classified as belonging to the symptom-complex of neurasthenia.

HEART AND PERICARDIUM

Acute Endocarditis.—The bacterial origin of acute endocarditis is now universally admitted. From the standpoint of focalized infections the division into “simple,” “verrucose,” “vegetative,” “malignant” and “ulcerative” is unimportant, except for convenience in describing the severity of clinical symptoms and of the end pathological changes. The gradations are merely evidences of the degree of virulence and specific pathogenicity of the infecting organism and of the lack of tissue resistance. Acute endocarditis may occur as the one demonstrable lesion secondary to a primary focus of infection, but is usually seen as a secondary local manifestation in the course of such diseases as rheumatic fever, chorea, tonsillitis, pneumonia, typhoid fever and gonorrhea.

The bacteria most frequently isolated from the blood and from the localized lesions in the heart-valves are the various members of the streptococcus-pneumococcus group, the staphylococcus and the gonococcus. The diphtheroid organisms, the *Bacillus coli communis* and other pathogenic microorganisms have been found to be less frequent etiologic agents.

The production of endocardial infection is embolic in character, the

bacteria lodging in the capillaries of the valves, the secondary lesions depending upon the degree of virulence of the organisms and the nature of the tissue reaction. The acute endocarditis associated with rheumatic fever is usually mild in type because of the low degree of virulence of the *Streptococcus viridans* which is the type of organism most frequently found to be the etiologic agent in this disease. Instances of destructive changes produced by this type of organism when it possesses increased pathogenicity have been noted. In infections due to the *Streptococcus mucosus*, the pneumococcus and gonococcus, destructive valve changes are apt to occur and the clinical symptoms of an acute malignant infection are present. Such types are seen complicating puerperal sepsis, septic wounds, acute gonorrhea and virulent infections of the nose and throat.

Chronic Endocarditis.—Chronic “progressive” or “recurrent” bacterial endocarditis, sometimes inappropriately termed “chronic malignant endocarditis,” is commonly the result of a simple acute rheumatic endocarditis in which the primary feeding focus of infection persists, the heart valves becoming less resistant to the chronic bacteremia because of the sensitization and the increased vascularity of the tissues, and the infecting agent becoming less virulent but apparently developing increased selective affinity for those tissues. This chronic form of endocarditis, however, may arise insidiously without the occurrence of acute manifestations such as acute rheumatic fever and be unrecognized until the subacute manifestations in its terminal stages evidence a form of intoxication suggesting body reaction to bacterial invasion. Both the recurrent type secondary to acute endocarditis and the slowly progressive type are due to a persistent low grade bacteremia, the *Streptococcus viridans* usually being the infecting agent.

The work of numerous observers* has established the etiologic relation of bacteria to this chronic form of endocarditis. At present it is the consensus of opinion that the types of organisms described by the various authors as the “*endocarditis coccus*,” “*diplococcus endocarditis*,” “*pneumococcus endocarditis*” and “*saprophytic streptococcus*” all apply to the viridans type of the streptococcus as described by Schottmüller, an organism possessing a low degree of virulence for the experimental animals and exhibiting a marked tendency to change its pathogenicity under cultural and animal passage conditions.

The clinical symptoms of this type of endocardial involvement are usually mild at its inception and may so continue for weeks and even months. At first there may be no noticeable manifestations other than a gradual lessening of strength, mild digestive disturbances, exhaustion and tendency to dyspnea upon exertion and nervous irritability—a symptom-complex often diagnosed as neurasthenia. There may be an accompanying slight variation in the diurnal temperature above the normal average. During this period, if previously there has been no acute endocarditis with permanent secondary valve destruction, endocardial murmurs may be absent. As the infectious process progresses,

* Billings; Horder; Lenhartz; Libman; Osler; Osler; Rosenow; Schottmüller.

variations in temperature may suggest malaria and when, associated with pulmonary symptoms as dyspnea, cough and expectoration, may suggest pulmonary tuberculosis. Later the febrile course of the disease may become more or less continued in type with at times, however, remissions, intermissions, chills, sweats, increasing weakness, loss of weight and anemia. Splenic enlargement is sometimes present which with the symptoms just described often leads to an incorrect diagnosis of typhoid fever. In the later stages the malignant symptoms develop in the form of embolic infections to the kidney, producing hemorrhagic glomerulonephritis, to the spleen, to the brain, to the skin, producing petechiæ, and to the lungs, causing death. The endocardial lesions early are of the nodular type, but as the disease progresses vegetations form. Thrombi are numerous and not only form a favorable medium for the growth of the bacteria but are the source of the embolic manifestations in the malignant stage of the disease. It is this persistent infection of the heart valves that makes the prognosis of these cases so unfavorable, since in this stage the removal of the original source of the infection may have little effect upon the localized valve infection. Billings looks upon a chronic *Streptococcus viridans* endocarditis as usually fatal and suggests that the cases reported as recovering may be those in which there exists an endocardial murmur from a previously healed endocarditis and a *Streptococcus viridans* bacteriemia but without a true active endocarditis. Healing of vegetations, however, has been noted at autopsy and clinical observers have reported recoveries.

The history of tonsillitis and sinusitis and the existence of dental abscess are of particular significance in the diagnosis of this disease.

Acute Pericarditis.—Acute pericarditis may occur alone under similar etiologic conditions as noted in infections of the endocardium or may be associated with an endocarditis. Its occurrence during the course of endocarditis is merely evidence of further metastases of bacterial emboli. Dependent upon the specific pathogenicity of the invading bacteria, the secondary changes may be mild or severe.

Chronic Pericarditis.—Chronic pericarditis is most frequently secondary to an acute infection but may arise as an independent lesion or coincident with a chronic endocarditis.

SEROUS MEMBRANES

Acute Pleuritis.—The demonstration in animal experimentation of the hematogenous invasion of the pleura by bacteria of specific pathogenicity is lacking, due to the fact, as shown by W. S. Miller, that in the rabbit, guinea pig and dog the pleura does not have a direct blood supply. In man, however, the pleura receives its blood supply through the bronchial artery. This fact, together with the frequent clinical observations of a fibrinous, serofibrinous or purulent pleuritis, occurring suddenly in the course of an acute nasal and throat infection without any demonstrable lung involvement, warrants considering pleural infection as one of the possible lesions secondary to hematogenous

invasion from a primary focal infection. Irons and Marine, in a recent study of streptococcal infections at Camp Custer, believed that while in some cases the primary infection reached the pleura by extension from a bronchopneumonia, in others the origin was hematogenous with secondary pulmonary involvement. Alexander also reports that purulent pleuritis occurred in 30 per cent. of pneumonias under his observations, but that the same lesion occurred secondary to other foci such as angina and tonsillitis. The work of Miller and Dunham on the lymphatics of the lung and their relation to tuberculous infection of the pleura is evidence against primary hematogenous pleuritis due to the *Bacillus tuberculosis* and supports the belief that this form of invasion by other pathogenic microorganisms is rare.

The various members of the streptococcus-pneumococcus group and the *Bacillus tuberculosis* are the most frequent types of organisms isolated from infections of the pleural cavity. The prevalence of empyema among soldiers in the various cantonments, during 1917-1918, according to the various observers (Alexander, Cole, Irons), was due to the *Streptococcus hemolyticus*.

Acute Peritonitis.—Acute peritonitis occurs, most commonly, secondary to infections in adjacent serous cavities or in any of the abdominal viscera, but hematogenous infection of the peritoneum, producing what may be termed a primary peritonitis, is not infrequent. In 106 cases of acute peritonitis, Flexner found that 12 had occurred independent of any pathological condition in the contained organs. He termed these *primary* and found bacteria present in 10 cases, in which 9 showed only a single infecting agent. In a series of 34 cases of peritonitis, in which the infecting bacteria apparently invaded the body at some point outside of the gastro-intestinal tract, Flexner found a single infecting agent in 25 cases and a mixed infection in 9 cases. The *Staphylococcus aureus* was found to be the most common infecting agent, while the *Streptococcus pyogenes* was next in frequency. The finding of the *Bacillus coli communis* was considered as evidence of invasion from the intestinal tract. Irons and Marine report two instances of apparent primary hematogenous invasion of the peritoneum with the *Streptococcus hemolyticus*. An hematogenous invasion of the peritoneum probably may take place from a primary focus of infection in any portion of the body.

JOINTS AND BURSÆ

Acute Infectious Arthritis.—Acute hematogenous invasion of the joints by bacteria from foci of infection most commonly located in the nose, throat or oral cavity, but at times at other portals of entry, has been definitely established by abundant experimental and clinical evidence. The character of the local pathological changes in the joints and of the associated lesions in other tissues depends upon the virulence and the specific pathogenicity of the invading microorganisms. The organisms of higher virulence in the streptococcus-pneumococcus group

produce violent tissue reaction and usually suppuration. Such organisms usually do not exhibit a specific elective affinity for joint tissue. The gonococcus, however, does possess a certain degree of specific affinity for joint tissue and is apt to produce the more severe type of tissue reaction. The synovial membranes of the joint, bursæ and tendons are usually involved with a serofibrinous and often a purulent effusion. The metastasis usually takes place during the acute manifestations of gonorrhea, but may occur during the subsidence of the acute symptoms or secondary to a chronic latent and oft-times undiscovered focus of infection.

The organisms of lower virulence in the streptococcus-pneumococcus group, namely, the *viridans*, the *gray* and *indifferent* and the *slightly hemolytic* forms (as shown in Fig 2) are those which usually possess specific joint affinity. These organisms produce the mild form of joint changes seen in *acute rheumatic fever*, and have been designated as the *Diplococcus*, *Micrococcus* and *Streptococcus rheumaticus* by different observers because of morphological variations. The original work of Poynton and Paine, and that of Beattie, of Walker and Ryffel and of Rosenow, has definitely established the etiologic relation of primary foci of infection to the acute arthritis of rheumatic fever and the other secondary manifestations of this disease, namely, acute endocarditis, acute tenosynovitis, acute myositis, acute myocarditis and acute pericarditis.

While these manifestations of acute rheumatic fever arise during the course of an acute nasal, tonsillar or dental infection, the frequent absence of such local inflammation and the tendency to the recurrence of rheumatic attacks indicate that latent foci of infection, containing bacteria of such a low degree of virulence that local reaction is not demonstrable, may suddenly develop that specific pathogenicity and degree of virulence necessary to cause the secondary lesions observed in rheumatic fever. That such latency of infection may occur has been discussed by Kolle and Wassermann and is suggested by the isolation of streptococci from the blood of patients free from clinical manifestations of an existing infection. The removal of diseased tonsils, the establishment of adequate drainage for the relief of chronically infected nasal sinuses and the extraction of abscessed teeth have been followed by a subsidence of the recurrence to attacks of acute arthritis.

In the acute non suppurative arthritis associated with rheumatic fever, the synovial membranes are hyperemic, showing occasional small hemorrhagic extravasations, and with a turbid effusion containing delicate flakes of fibrin. The tendency in such joints is to heal, leaving little or no trace of the infection. These are the characteristics of all the acute serous membrane infections due to the *Streptococcus viridans*. It is true, however, that in the severe forms of rheumatic fever this organism sometimes possesses that degree of virulence necessary to produce an exudative or ulcerative process, secondary proliferative fibrosis resulting.

Chronic Infectious Arthritis.—The focal origin of chronic inflammation of joints due to the *Bacillus tuberculosis*, the gonococcus or the

Treponema pallidum has been universally accepted. Opinions as to the etiology of chronic arthritis due to other causes than the above, however, have been widely variant, due mainly to the exhaustive study of the end pathological changes rather than a consideration of the primary etiologic factors responsible for these changes. The evidence at hand is to the effect that chronic inflammations of the joints exhibiting either exudative, proliferative or degenerative changes are not distinct diseases but represent the type and stage of the reaction of the tissues to the original and various contributing causes. The evidence at the same time suggests that the primary causal factor is bacterial infection and that the metabolic changes so noticeable in certain forms of chronic arthritis are secondary manifestations. The bacterial infection is probably always hematogenous and is secondary to a persistent focus of infection in which the microorganisms are of the lower degree of virulence and possess an elective tissue affinity for the joint structures.

Bacterial emboli to the terminal vessels of the joint tissue produce a primary endothelial proliferation with secondary plugging of the vessels with cells and hemorrhagic infarctions, the organisms multiplying within the endothelial proliferation, and the triangular region of the infarction. In the more virulent types a serofibrinous exudate may result. When the organisms are of low virulence they are either destroyed, their endotoxins producing local irritation, or there is a tendency to "walling off," both processes being followed by secondary proliferative fibrosis. This tissue reaction, the formation of obliterating thrombi in the smaller vessels, interferes with the blood supply of the articular and periarticular tissues, bringing about, as Billings points out, the metabolic changes necessary to the production of either the proliferative or the degenerative types of arthritides described by Nichols and Richardson. The interference to the blood supply of joints was suggested by Axhausen as a factor in the production of the anatomic changes in arthritis deformans. The infection to the joint may invade the synovial membranes, the ligaments, the capsule, the articular cartilage and the bone, producing the hypertrophic or atrophic changes resulting in the various anatomical and clinical types of arthritis deformans (rheumatoid arthritis, osteo-arthritis).

In the later proliferative and atrophic stages bacteria may not be found in the joint tissues, the progressive processes being due to the disturbed local metabolism brought about by the primary reaction to the bacterial invasion, but may be demonstrated in the lymph-glands draining the involved joints.

The etiologic relation of chronic focal infection to chronic arthritis is established. Chronic infections of the tonsils, sinuses, teeth, genito-urinary tract in both sexes, gastro-intestinal tract and bronchial glands have been found as probable causes in a vast number of cases. The incidence of focal infection in chronic arthritis is rather constant. Langstroth reports that in 73 per cent. of cases a chronic focus was demonstrated, while 15 per cent. had probable foci of infection. In our series of 50 cases a chronic focus of infection was actually demonstrated in



A



B

FIG. 6, A AND B.—ROENTGENOGRAMS OF A CASE OF SUBACROMIAL BURSITIS OF TWELVE YEARS' DURATION.

The predisposing factor in this case was apparently trauma. A shows the condition prior to dental correction; B, that one month after dental infection was eradicated. Note in the first picture a well-marked density under the acromion. In the second picture this density has become hazy, except for the central nucleus.



C



D

FIG. 6. C AND D.—ROENTGENOGRAMS OF A CASE OF SUBACROMIAL BURSITIS OF TWELVE YEARS' DURATION.

C shows the condition existing two months after the dental infection was eradicated; D, that three months after the eradication. Note that in C the density under the acromion has almost disappeared. In D it can no longer be seen.

100 per cent. One focus of infection was determined in 24 per cent., two foci in 44 per cent. and three or more foci in 32 per cent. The location of these foci was as follows: dental 70 per cent., nasal 60 per cent., tonsillar 35 per cent., gall-bladder 4 per cent., appendiceal 6 per cent. Soper states that 7 out of 50 cases of rectal and sigmoid infection showed arthritis deformans. In a study of 47 cases at Cook County Hospital, Irons found that alveolar abscess in 75 per cent., infection of tonsils in 45 per cent., syphilis in 23 per cent. and other chronic infections in 21 per cent. were the focal infections determined in arthritis.

The streptococcus possessing a low virulence and a high degree of sensitiveness to oxygen belonging to the *viridans* or the *gray and indifferens* group is the most common etiologic agent, though the gonococcus and *Bacillus tuberculosis* must always be considered.

The tendency to localization in the joint tissues of these organisms of low virulence, persisting even after the removal of the primary focus of infection, explains the progressive character of chronic arthritis in many cases. These organisms probably develop a special joint tissue affinity because of their growth in joint tissue in accord with the experimental observations of Forssner, who reports that streptococci grown on kidney tissue develop special affinity for kidney tissue when injected intravenously into animals. Persistent infection in one joint, therefore, may lead to the secondary involvement of other joints by hematogenous metastasis from joint to joint.

Tenovaginitis and Bursitis.—Similar infective processes may effect the tendinous insertions of muscle, producing tenovaginitis. Inflammations of the bursæ mucosæ and the bursæ synoviæ are frequent occurrences. Traumatism may be the cause of painful bursal swellings, but an inflammatory process is probably secondary to direct or hematogenous bacterial invasion to which trauma may be contributory. The synovial bursæ around joints are usually infected coincident with joint infections, since they usually connect with the joint cavity, but the acute and chronic inflammations of the synovial bursæ between muscles is probably secondary to hematogenous infection, trauma playing an important rôle in the location of the lesion.

As an illustration of bursal infection and the possible secondary results, the studies by Codman and by Brickner on chronic subacromial bursitis with and without calcareous deposit are interesting. This condition is one of the common causes of painful shoulder. The latter author emphasizes the traumatic etiology of this condition and believes that an etiologic bacterial factor has never been substantiated. The descriptions of the pathological changes, however, are similar to the changes in other synovial membranes secondary to a *viridans* infection.

As illustrating a possible etiologic relation between dental foci and subacromial bursitis, the roentgenograms (Fig. 6) of a case of several years' duration show a gradual absorption of the calcareous body following the extraction of teeth without other remedial measures being instituted. The failure to find bacteria either in the calcareous substance or in the fluid of the bursal sac is to be expected, since the bac-

terial invasion of and localization in synovial membranes is within the tissues themselves, the other manifestations being secondary to locally disturbed circulation and metabolism.

We have noted subacromial bursitis as a frequent acute manifestation complicating acute nasal and throat infections in individuals, however, who gave a history of previous trauma. The recurrence of pain and limited function following recurrent acute infection has also been noted. In one case of multiple calcareous bursitis, complete freedom from pain and from limitation of motion was not observed following the removal of foci of infection because of the presence of an old fracture and misplacement of the coracoid process.

SKIN MANIFESTATIONS

Manifestations apparently occur as the result of metastases to the skin of microorganisms possessing special pathogenicity.

Erythema Nodosum.—Erythema nodosum has been noted as a complicating symptom in acute chorea, cerebrospinal fever, acute rheumatic fever, and as a part of the symptom complex of erythema exudativum multiforme described by Osler. It also occurs independently of any acute infectious disease and unassociated with articular or visceral involvement. It has frequently been noticed by the author in young adults following the subsidence of an acute tonsillitis, the patient showing evidence of chronic infection of the tonsils. In some cases it has been associated with marked febrile reaction while in others the only clinical manifestations were the skin lesions. In one of the cases lasting over a period of months there was a more or less general myositis, different groups of muscles being involved in sequence following the subsidence of acute symptoms in the preceding group. The removal of a focus of infection usually brings about relief from symptoms and their recurrence. In the case which lasted over months, even after the removal of the infected tonsils, the progressive infection of groups of muscles may be explained on the basis of the development of muscle tissue affinity on the part of the bacteria because of the persistent focus in muscle tissue.

The type of organism usually isolated in cases of erythema nodosum belongs to the group of low virulence, but as shown in Fig. 2, it approaches the type of the more virulent and hemolytic forms. The diphtheroid organisms have been demonstrated in the blood and in the nodes in patients with erythema nodosum. Erythema nodosum, therefore, should be looked upon as a symptomatic lesion of infection associated at times with other inflammatory changes in the body, but at times the only manifestation secondary to an acute bacterial invasion or to invasion from a persistent focal infection.

Petechiæ and Ecchymoses.—Petechiæ and ecchymoses diagnosed as infectious or arthritic purpura, frequently seen as manifestations in various infectious diseases and blood dyscrasias, are purely symptomatic and indicate degenerative changes in the small blood-vessels and capil-

laries of the skin. Christian reports upon a series of ten cases showing various skin manifestations in the form of purpura, erythema, urticaria and angioneurotic edema and various visceral lesions, as hematuria, disturbed renal function, arthritis and gastro-intestinal disturbances. He states that the pathology consists of transitory focal lesions of the small blood-vessels and capillaries, but offers no explanation for the etiology of the condition other than to suggest a similarity to certain anaphylactic manifestations. Our present knowledge of the etiologic relation of focal infections to arthritis, nephritis and certain anaphylactic manifestations based upon clinical observation and animal experimentation permits the hypothetical deduction, at least, that, in the absence of other causes, purpuric lesions may be secondary manifestations of persistent localized infection at or near a portal of entry which through the bacterial endotoxins acting as a foreign protein bring about degenerative changes in the blood-vessels. Such manifestations necessitate the careful examination of such patients for focalized infection. In the author's experience the removal of infected teeth and diseased tonsils and the drainage of a chronic ethmoiditis have been followed by a disappearance of the skin manifestations, renal disturbances and secondary anemia.

Urticaria.—Urticaria is frequently noted as a recurrent manifestation in individuals with evident chronic nasal, tonsillar or dental infections and with suspected chronic gall-bladder and appendiceal infections and has been improved by the removal of such infections.

ACUTE AND CHRONIC INFECTIONS OF THE GASTRO-INTESTINAL TRACT

Acute Appendicitis.—The focal origin of acute appendicitis is supported by abundant clinical and experimental evidence. That it is an infection secondary to the hematogenous invasion of bacteria from foci of infection and not the result of primary invasion of the infective agent from the lumen of the organ is maintained by several observers.* Local stasis, foreign bodies and involutional changes in the appendix are undoubtedly factors in the production of appendicitis,** but only as predisposing to lessened resistance against metastatic focalization in that organ.

Various authors have noted the apparent etiologic relation of nose and throat infections to acute appendicitis. Kretz showed that streptococci from such foci invaded various tissues and organs, among them the appendix. Canon also emphasized the hematogenous origin of appendicitis. Adrian noted the relation of angina and bacteriemia to appendicitis. Ghon and Namba concluded from their observations that if appendicitis was the result of hematogenous infection, it must be due to a specific strain of streptococcus.

The recognition of an apparent relation of the prevalence of acute appendicitis to the incidence of acute nasopharyngeal and tonsillar infections and the occurrence of the disease in epidemic form has been

* Adrian; Canon; Ghon; Kretz.

** A. O. J. Kelly.

frequently noted * since the diagnosis of appendicitis has been more generally appreciated.

Evans reported upon the relation of the incidence of acute appendicitis to acute infections of the upper respiratory and the upper digestive tracts, based on the study of the morbidity of young adults over a period of six years. It was found that in 214 cases of acute appendicitis 86 per cent. had shown evidences of acute nasal and throat infections on an average of sixteen days prior to the appendiceal attack. It was also noted at eight periods during the six years of these observations that there were marked increases above the expectant rate which evidenced an epidemic type of the disease and indicated a widespread infection with organisms having a special tissue affinity for the appendix. During such periods appendicitis occurred from 4 to 15 times above the expectant rate and the interval between the nasal and throat infections and the appendicitis was on an average of 8 instead of 16 days. It was also noted that of the 12,000 individuals under observation for acute respiratory infections only 1.1 per cent. developed acute appendicitis, while of those observed during any of the periods of epidemic 3 to 3.5 per cent. developed that disease. During the epidemic periods 93.7 per cent. of the appendicitis cases showed upper respiratory infection, while only 10 per cent. of the total population of the University of Wisconsin exhibited such infection.

A streptococcus in the lower group of virulence is the most frequent infecting agent in appendicitis. The presence in the tissues of a diseased appendix of organisms having their normal habitat in the intestines has been noted by Heyde and Aschoff, the latter placing great importance upon a primary mechanical factor in the production of appendicitis as predisposing to direct bacterial invasion. The evidence at hand at present makes it seem more probable that these bacteria invade the appendix secondary to the hematogenous invasion of a member of the streptococcus-pneumococcus group. Diphtheroid organisms are not infrequently found as the only infecting agent in appendices.

Chronic Appendicitis.—Chronic infection of the appendix is usually secondary to acute appendicitis. It may occur, however, as a low grade progressive infection secondary to a primary focus of infection of very low virulence.

Acute Cholecystitis.—While direct bacterial invasion of the gall-bladder may occur, as is frequently the case in an infection from the *Bacillus typhosus* and the *Bacillus coli communis*, yet it is more often hematogenous in origin. The primary seat of infection is usually in the nose or throat. It may occur, however, secondary to the involvement of the lymphatics of the intestine and mesentery or by the hematogenous invasion of the *Bacillus typhosus*, the *Bacillus coli communis*, or the streptococcus invading the intestinal canal and involving the lymph-nodes. Bacterial metastases to the gall-bladder lodge in the terminal vessels of the fundus, the organisms invading the hemorrhagic area that is produced by the blocking of the blood-vessels with a thrombus-like

* Hood; Mantle; Martin; Marvel; Rosenow and Dunlap; Rostowzew; Wahle.

collection of leukocytic and proliferated endothelial cells. Extension from this area to the mucosa is followed by a cholecystitis, either acute or chronic, depending upon the virulence of the organism. The infection brings about the precipitation of bile salts when the bile is concentrated and of high cholesterin content, the latter factor being particularly emphasized in the etiology of the formation of gall-stones by Aschoff and Hennes. Both Kretz and Canon contend that cholecystitis is hematogenous in origin, the latter believing that this is true even when the *Bacillus typhosus* is the infecting agent.

The occurrence of acute cholecystitis following acute nasal and throat infections and after the subsidence of an unoperated acute appendicitis has been a rather frequent observation of the author. The interval between the gall-bladder manifestations and the subsidence of the acute infections of the nose and throat was somewhat longer than that noted in the appendicitis cases. During some of the periods of epidemic appendicitis just described, the prevalence of acute cholecystitis with jaundice was noted. It was also observed that, in a few cases of unoperated appendicitis, gall-bladder symptoms occurred following the subsidence of the former. These clinical observations support the laboratory evidence of an apparent increase in virulence of streptococci infecting the gall-bladder as compared with those infecting the appendix.

The most common bacteria isolated from the gall-bladder are *Bacillus coli communis*, *Bacillus typhosus*, members of the streptococcus-pneumococcus group and staphylococcus.

Chronic Cholecystitis.—Chronic inflammation of the gall-bladder usually is the continuation of an infection following the subsidence of acute cholecystitis; it may, however, arise as the result of the invasion of an organism whose virulence is such that an acute tissue reaction is not produced. Clinically, many cases of chronic cholecystitis, with or without gall-stones, occur in which a history of previous acute gall-bladder symptoms is not obtainable. It is probable that a low grade of infection similar to that described in chronic infectious arthritis takes place. In such cases of chronic infection the focal infections from which the bacterial invasion has taken place are also chronic and produce little or no local manifestations.

Acute Gastric and Duodenal Ulcer.—The occurrence of gastric and duodenal hemorrhages during the course of acute infectious diseases and the association of gastric and duodenal ulcers with severe anemias and chlorosis, together with the prevalence of such persistent foci of infection, as chronic tonsillitis, pyorrhea, dental abscess, and chronic sinusitis in cases of ulcer of the stomach and duodenum, suggest both a toxic and infectious etiology of these ulcerations. Bolton calls attention to the incidence of pyorrhea in such cases and Langstroth reports clinical evidence of chronic focal infection in 84 per cent. of the ulcer patients examined. Billings notes the improvement in symptoms in ulcer cases following the eradication of foci of infection. The occurrence of acute manifestations in chronic ulcers or the development of symptoms of primary ulceration following the subsidence of acute

nasal, throat or dental infections and the apparent close clinical relation between infections of the appendix and the incidence of gastro-duodenal ulceration suggests more definitely the bacterial causation of these conditions.

The bacteriologic findings of Rosenow and Sanford, in a study of ulcers of the stomach and duodenum in man, adds still greater evidence that the streptococcus, in particular, is commonly an important primary etiologic factor in the production of gastric and duodenal ulcer and not merely an accidental secondary invader of the tissues. They found streptococci in pure culture in nine instances and in cultures mixed with either staphylococci, *Bacillus welchii* or *Bacillus coli communis* in 14 instances in 24 ulcers. In the stained sections of 47 ulcers, diplococci and streptococci were found in 36 instances. The production of ulcers of the stomach and duodenum by injection of streptococci of a certain grade of virulence and the recovery of this strain from the ulcer and surrounding tissues is the strongest evidence at hand that such ulcerations may occur as the result of bacterial metastases. The incidence of gastric ulcer to appendicitis and cholecystitis in this series of experiments showed that where the virulence of the streptococcus was increased it developed an increased affinity for the gall-bladder and when decreased showed an increased affinity for the appendix. The infecting agent, therefore, belongs to the group of lower resistance in the position as designated in Fig. 2. The observations of Gerdine and Helmholtz as to the infectious origin of duodenal ulcer in children confirm these laboratory observations.

Chronic Gastric and Duodenal Ulcers.—These are most frequently secondary to acute ulceration due to a continued infection of the tissue surrounding the ulcer which prevents healing. It is possible, however, that the infection may be of such a low grade of virulence, that a chronic ulcer may result without any intervening acute symptomatology, since it is not infrequent that chronic ulcerations are found in individuals who have never suffered with the symptoms associated with acute ulceration.

Intestinal Infections.—Reference has been made to Soper's observations of the relation of infections of the mucosa of the rectum and sigmoid to secondary systemic and visceral manifestations. It was pointed out that, while this infection localized in the mucosa of the intestinal tract might be the result of direct primary invasion, it might also be the result of hematogenous invasions from foci outside of the tract and be merely a part of general secondary changes noted in these cases rather than the site of the primary etiologic focus. This demonstration of infection of the mucosa and Preston's report of cases pointing to purulent infection as a causative factor in mucous colitis are evidences of the probable etiologic relation of foci of infection in the nose, throat and teeth to acute and chronic gastro-intestinal infections. Preston noted that the correction of a frontal sinusitis, an ethmoiditis or a dental infection brought about a subsidence of the intestinal symptoms. He concluded that the infection acted upon the autonomic nervous system rather than directly upon the bowel.

From all evidence it seems that acute gastro-intestinal condition may arise secondary both to direct bacterial invasion and to hematogenous invasion from far distant foci. It is at least necessary in all such conditions to attempt to determine the existence of primary foci and to correct them if possible.

Acute Interstitial Pancreatitis.—Acute interstitial pancreatitis is probably always due to bacterial invasion of the organ. Many authors emphasize the importance of ascending infection by way of the pancreatic duct. The experiments to prove this mode of infection have resulted in the production of the suppurative type of interstitial pancreatitis or pancreatic abscess. Opie states that occasionally the pancreas may exhibit an acute interstitial inflammation without suppuration and in a case reported believes it probable that the infection was an ascending one secondary to acute inflammation of the stomach and duodenum. Opie draws a clear line of distinction between such an acute pancreatitis and the acute hemorrhagic pancreatitis or hemorrhagic necrosis, the experimental work and autopsy findings indicating that the latter is associated with bile and pancreatic juice stagnation within the organ.

The evident association of cholecystitis and cholelithiasis with acute hemorrhagic pancreatitis led many to believe that the invasion of bile into the pancreas as the result of impaction of calculi was the cause of the latter. This belief has been supported by laboratory experimentation. The demonstration of the hematogenous bacterial infectious origin of cholecystitis, cholelithiasis, gastric ulcer and appendicitis and the occasional occurrence of symptoms of acute pancreatic disturbance, in association with epidemic parotitis in a manner similar to the metastatic lesions to the testes in that disease, suggests the possibility of a more frequent metastatic infectious origin of acute pancreatitis than was previously believed.

The production of non-suppurating lesions in the appendix, stomach and gall-bladder and the evidence that the invasion of these tissues depended upon a certain degree of virulence of the streptococcus suggested that a still greater degree of virulence is necessary for the development of a special affinity for the pancreas. There is evidence which at least suggests the probability of frequent inflammation of the pancreas in the course of infectious disease which is neither suppurative nor necrotic in character and which subsides coincident with the other bacterial process. The changes secondary to the disturbed circulation produced by bacterial emboli may bring about certain of the chronic progressive degenerative processes that are associated with disturbed metabolism as in diabetes mellitus.

EYE INFECTIONS

There is sufficient clinical evidence to establish focal infections, especially nasal, tonsillar, or dental, as one of the important etiologic factors in the production of inflammatory diseases of the eye. Eye complica-

tions of acute tonsillitis, acute sinusitis or acute dental infection are not infrequent. Various observers* have attributed conjunctivitis, phlyctenular keratitis, interstitial keratitis, iritis, iridocyclitis, uveitis, episcleritis, choroiditis, retinitis and optic neuritis to acute and chronic infections of the accessory sinuses, tonsils and dental structures. The members of the streptococcus-pneumococcus group and the meningococcus have been the organisms most frequently reported as causal infecting agents, though the colon bacillus and staphylococcus have been found to possess special pathogenicity for the eye in animal experiments. Tuberculous iritis has been attributed to tuberculous adenoids. Irons and Brown, in a study of 100 cases of iritis, report the etiologic factors to be: syphilitic in 23, gonococcal in 9, tuberculous in 8, dental infection in 18, tonsil infection in 16, sinus infection in 3, non-venereal genito-urinary infection in 3, other suppurating infections in 2, infections so combined that the etiologic factor could not be determined in 17, and no etiologic factor in 1. The associated lesions in experimental animals injected with streptococci isolated from cases of rheumatic arthritis and myositis are those usually seen in man, namely: unilateral panophthalmia, hemorrhages on the limbus with or without episcleritis, conjunctivitis, ulcer of the cornea, arthritis, appendicitis, gastric ulcer, endocarditis, pericarditis, myositis and nephritis. Inflammatory disease of the eye demands careful search for focal infections, even if syphilis, tuberculosis, or gonococcal infections are present.

THYROID GLAND

Thyroiditis.—Enlargement and tenderness of the thyroid gland arise so frequently during the course of acute infectious diseases that several observers, especially of the French school, attribute such manifestations to an inflammation of the gland. Vincent reports that from 66 to 68 per cent. of his patients with acute rheumatic fever showed evidence of thyroid reaction which he attributed to hyperfunctioning of the gland as a part of the general body reaction against the infection. Others (Albertin, Sougnes, Weintraud) have reported similar observations of symptoms of hyperthyroidism in acute rheumatic fever. Evidence of actual infection of the gland is lacking. In our own observations we have noted the great frequency of apparent hyperfunctioning of previously quiescent thyroids during acute tonsillar and nasal infections, which usually subsided coincidently with the acute manifestations of such infections. In a study of tonsillar entamebiasis and its relation to thyroid manifestations, Evans, Middleton and Smith noted that the removal of the entamebic infection was accompanied by a decrease in size of the gland in colloid goiters and a decrease in the symptoms of hyperfunctioning in the exophthalmic type. We concluded, in the absence of evidence of infection in glands studied, that dysthyroidism in these cases was due to a reaction against toxemia and that the

* C. C. Boyle; H. Collette; Dunn; E. E. McCown; Schenck; H. M. Thompson; L. E. White.

entamebæ might play a symbiotic rôle. From the clinical standpoint alone there is no doubt but that some patients exhibiting symptoms of hyperthyroidism improve following the eradication of persistent foci of infection.

GENITO-URINARY TRACT

Nephritis.—Various observations both clinical and experimental have established the fact that bacterial infection may be one of the causes of acute and chronic nephritis. The frequent occurrence of inflammation of the kidney during the course of infectious diseases and the demonstration of the specific organism of the disease in the urine led many clinicians* to believe that a certain type of non-suppurative nephritis is due to bacterial invasion of the kidney.

Nichols, in 1899, in 45 cases of chronic nephritis of all forms found diplococci in 29 and bacilli in 4. In 1910 Löhlein suggested that the glomerular kidney lesions complicating malignant endocarditis due to the *Streptococcus viridans* might be due to bacterial emboli to the glomerular tufts. Baehr later described the renal changes found in animals injected with the streptococcus from subacute "bacterial" endocarditis. He found that in most cases there were bacterial emboli to some of the glomerular tufts producing distinct pathological lesions in the involved glomeruli without evidence of disease either in the uninvolved glomeruli or in the uninvolved portion of the affected glomeruli. Evidence of rapid healing was coincident with evidence of a similar process in the endocardial lesions. The symptoms and end pathological changes were in direct proportion to the number of glomerular lesions. If few lesions existed, hematuria was the only noticeable symptom and healing took place if the bacteriemia subsided; but if the glomerular lesions were numerous, there was either a rapidly fatal subacute hemorrhagic nephritis or, with the healing of the endocardial lesion, a secondary contracted kidney ensued, producing typical symptoms and death.

Le Count and Jackson have also shown similar renal changes in rabbits injected with streptococci. They noted the same embolic glomerular involvement and the same tendency to rapid healing. Rosenow found that kidney lesions were common in those animals injected with streptococci from rheumatic fever, especially after animal passage, the lesion occurring in the medullary portion, and in those animals injected with streptococci from endocarditis, the lesions being glomerular in type.

Ophüls describes glomerular nephritis as being acute, subacute and chronic. The acute stage is produced by septic infection associated with endocarditis and may be of the focal hemorrhagic type described by Baehr when the infection is overwhelming. The subacute stage is that occurring after a tonsillitis or other local streptococcic infection. In the chronic stage it is difficult to discover the original focus of infection, but the history of such cases is always significant in that there has been a recent localized infection.

* Adami; Baehr; Billings; Grulee; Klotz; Ophüls; Stengel.

It is always evident, according to Ophüls, that the subacute and chronic stages in children are secondary to infection. Grulee and Gaarde also emphasize etiologic relation of infection to a form of hemorrhagic nephritis occurring in children usually following 6 or 7 days after an acute tonsillitis, cultures from the blood and throat corresponding with those from the urine.

Others have noted the evidence of the bacterial causation of nephritis. G. F. and G. R. Dick found that bacteria isolated from urine of nephritis may produce the urinary and anatomic findings of nephritis and point out the importance of the etiologic relation of foci of infection to acute and chronic kidney disease. Billings has reported his clinical observations of the definite relation between focal infections and glomerulonephritis and the apparent subsidence of the renal symptoms secondary to the removal of the focus.

In the acute and early subacute stages of glomerular nephritis, streptococci and diplococci may be found in the urine and in the lesion, but in the chronic stage, the bacteria apparently have undergone lysis, the endotoxins producing the secondary pathological changes. In both the subacute and chronic stages, there is hypertension, continued definite urinary findings (lessened urine, albumin, casts, erythrocytes and leukocytes), and often uremia. Secondary anemia occurs early and is often associated with edema.

With this evidence at hand acute bacterial invasion from persistent focal infection must be given due consideration in the etiology of nephritis.

Pyelitis.—As already pointed out under sites of focal infections, pyelitis may occur as a hematogenous invasion secondary to a focal infection in the nose, throat or teeth. Bacilluria is emphasized as a basis for the diagnosis of pyelocystitis in children.

INFECTIONS OF NERVOUS SYSTEM

Neuritis.—The demonstration of localized hemorrhages, edema, leukocytic infiltration and diplococci in the peripheral nerves of animals injected with the pneumococcus isolated from foci of infection in cases suffering with multiple neuritis, and the demonstration of living streptococci in the pulp of a tooth and in the fascia and muscles of a patient suffering with recurrent attacks of dental neuritis and myositis, and the reproduction of tooth, nerve and muscle lesions in animals injected with this strain suggest that hematogenous bacterial invasion of the nerve trunks is one of the causes of neuritis in man. Exposure and trauma are important factors in the production of neuritis, but in many instances appear to be merely factors contributing to lessened resistance against infection and against the effect of bacterial endotoxins. Clinically, the occurrence of neuritis complicating a dental, tonsillar and nasal infection and the subsidence of the same following the removal of the foci of infection are frequently observed.

In our experience in dealing with young adults, acute neuritis has

been observed in 344 individuals. The most frequently noted possible etiologic factor was a recent acute nasopharyngeal infection, the signs and symptoms of the neuritis occurring on an average of eight days following the subsidence of such infections. In the more slowly developing and the more persistent type of neuritis, especially of the brachial and sciatic plexuses, a chronic focalized infection, dental, tonsillar or nasal in frequency in the order named, was discovered to be the etiologic factor. History of definite trauma was infrequent, but the localization occurred commonly in regions exposed to occupational tiring and traumatization. The preponderant occurrence of the inflammation of nerve trunks in the female in this series is interesting and suggests a sex predisposition.

Myelitis.—Hematogenous invasion of bacteria into the spinal cord has been recognized for a long time as one of the causes of myelitis. The type of myelitis produced by the bacterial invasion depends upon the anatomical localization and upon the character of localized reaction of the spinal tissues dependent upon the virulence of the infecting organism. The pathological changes are probably brought about by bacterial emboli to the terminal blood-vessels which produce a proliferation of and the formation of thrombus-like collection of endothelial cells. This obstruction of the capillaries is followed by minute hemorrhagic infarcts and secondary leukocytic infiltration. Changes in the nerve fibers and cells occur secondary to this interference with the normal blood supply and as a result of the action of the bacterial endotoxins.

Acute hematogenous myelitis occurs occasionally during the course of acute infectious diseases, as acute rheumatic fever, pneumonia, tonsillitis and gonorrhea, but occasionally it arises without any evidence of a general infection. In such cases the presence of a persistent localized infection should be determined. Acute bacterial invasion, however, may occur without producing local evidence at the portal of entry, the invasion of the nervous system being immediate.

The case of spinal insular sclerosis reported by Billings, in which Rosenow was able to isolate a streptococcus from the tonsils of the patient which produced focal hemorrhages in the spinal cord of injected animals, is sufficient to suggest the etiologic relation of such foci to spinal cord localization.

Acute Anterior Poliomyelitis.—Inflammation of the ganglion cells of the anterior horns and of the axons leading from them, occurring most frequently in young children either in sporadic or epidemic form, is believed generally to be due to hematogenous infection. Whether the view held by Flexner and others (Lewis, Noguchi, Peabody) that the disease is produced by a filterable virus and probably by a globoid organism isolated from the central nervous system in poliomyelitis, or that held by Rosenow and others (Hektoen, Mathers, Nuzum) that the disease is due to infection by a pleomorphic form of the streptococcus showing specific elective affinity for the anterior horns of the spinal cord, is accepted as explaining the true etiology of this

disease, its focal character is strongly suggested by the clinical observations in both the sporadic and the epidemic forms.

Flexner's production of anterior poliomyelitis by injection of the filterable virus in the nasal mucosa of animals and Rosenow's demonstration of the frequent presence of a pleomorphic streptococcus in the tonsils of patients with poliomyelitis, and the evident elective affinity of these organisms for the central nervous system of young animals, indicate that the upper respiratory and upper digestive tracts are probable portals of entry and sites of persistent focalization in this disease.

Acute Chorea.—The occurrence of acute chorea in scarlet fever, acute rheumatic fever, acute endocarditis, puerperal fever and gonorrhea suggests strongly the infectious origin of this disease. Its relation to acute rheumatic fever, and the frequent incidence of acute simple or vegetative endocarditis in chorea, indicates a common bacterial etiology. Chorea may occur in individuals in whom there is neither evidence of arthritis or endocardial lesion nor a history of such diseases in the past. It may precede, occur with or follow rheumatic fever. The infecting source, therefore, does not depend solely upon an arthritis or an endocarditis, but upon any focalized infection in the body which may cause bacterial emboli to the brain. The central localization probably depends in part upon the selective pathogenicity of the invading organism and in part upon the individual predisposition. The isolation of streptococci from the meninges in individuals having chorea (Rothstein) is suggestive of cerebral localization of bacteria. The experiments in which chorea was produced in animals by the injection of fine particles into the carotids support the embolic theory of the disease.

The removal of infectious foci in chorea has not always been followed by completely satisfactory results, probably due in part to persistent foci of infection in the brain and in part to the degenerative changes secondary to embolic and thrombotic processes.

Herpes.—The inflammation of the posterior ganglia and of the nerve trunks supplying definite skin areas usually results in the formation of papulovesicular lesions in those areas. This inflammation is generally conceded to be due to hematogenous bacterial infection of the ganglia and the nerve trunks. The incidence of herpes labialis in pneumonia of herpes facialis in tonsillar and dental infections and of herpes zoster in individuals harboring chronic foci of infection has been demonstrated and indicates that bacterial infection is the primary etiologic agent, while trauma and exposure to cold are predisposing factors contributing to special localization. In Billings' Clinic, Rosenow was able to reproduce herpetic lesions and streptococcal infections of the posterior root ganglia in animals injected with streptococci isolated from infected foci in patients suffering with herpes zoster.

INFECTIONS OF MUSCLE TISSUE

Myocarditis.—The occurrence of myocardial disturbances during the course of acute infectious diseases is common, especially so in acute

rheumatic fever. The belief that such changes were due alone to the effect of toxins upon the heart muscle has been modified by the experimental observations of Wachter, Bracht, Jackson and Rosenow, who have shown the presence of streptococci in the myocardium following the intravenous injection of these organisms into animals. The non-suppurating lesions produced by streptococci of low virulence are similar to the other lesions produced by the *Streptococcus viridans* in acute rheumatic fever, namely, a primary hyperemia with a tendency to hemorrhagic foci with secondary proliferative fibrosis and degenerative changes.

The important significance of cardiac irritability and of the "effort syndrome" in relation to endurance in army service shows the importance of determining the presence of persistent low grade infection in all cases in which the response to activity is associated with cardiac distress or irritability. The relation of such foci to rheumatic fever and endocarditis has been discussed in detail, the principle involved in infections of the myocardium being the same.

Myositis.—Infection of the skeletal muscles producing "muscular rheumatism," "myalgia" and myositis is common. In many cases of acute rheumatic fever of the more severe type, there is also muscular involvement. Instances of isolated muscle involvement associated with dental infections or in individuals with chronic foci of infection are observed frequently. That such manifestations may be due to actual infection of the muscle arising as the result of the hematogenous invasion of bacteria from a confined region of infection and that living organisms may be *latent* in the tissues during a period of freedom from symptoms has been demonstrated by Rosenow in a case of "pulpitis, dental neuritis and myositis." The incidence of localization in muscle tissue of streptococci isolated from cases of myositis and "myalgia," 71 per cent. and 93 per cent. respectively, strongly suggests the development of an elective affinity for this tissue on the part of members of the streptococcus-pneumococcus group. The type of organism usually invading the muscle is of that degree of virulence possessed by the organism producing erythema nodosum and belongs to the general group of lower virulence, as shown in Fig. 2.

In so-called "lumbago," when sacro-iliac sprain is excluded, and in "myalgia" the presence of infections of the nose, tonsils, teeth and genito-urinary tract should be sought.

INFECTIONS OF BONE TISSUE

Osteomyelitis.—Acute or chronic infectious osteomyelitis, while often due to direct bacterial invasion, the result of trauma, is most frequently caused by hematogenous infection either during the course of an acute infectious disease, from a persistent focus of infection or as the result of a chronic systemic infection as syphilis or tuberculosis. In acute osteomyelitis, the streptococcus, the staphylococcus, the *Bacillus typhosus* and the *Bacillus coli communis* have been found to be frequent invaders of bone tissue. The author has observed an acute osteomyelitis of the

middle of the femur secondary to a pelvic abscess due to the *Bacillus coli communis*, a bacteriemia having been demonstrated prior to the secondary localization. Chronic osteomyelitis may be an end product of an acute infection or may begin as a slowly progressing form of the disease due usually to tuberculosis, syphilis and typhoid infections.

TOXIC EFFECTS OF FOCAL INFECTIONS

As already pointed out, the manifestations of swelling and tenderness of the thyroid gland during the course of acute infectious diseases may be the result of a reaction against the toxins from a focalized infection rather than the result of an actual infection of the gland.

Anemia.—Anemia in varying degree is a rather constant condition associated with acute or chronic infection. The degree is apparently dependent upon the toxicity of the organisms especially as regards its hemolysing property. That bacteria may invade the bone marrow without producing suppuration is probable, but even if that occurs it is more likely that they are rapidly destroyed and that their endotoxins produce the faulty hyperplasia of the marrow seen in the severe types of anemia. The endotoxins absorbed from confined regions of infection may produce hemolysis in the circulating blood, necessitating an increased demand upon the blood-forming organs for more rapid production with the result that the infantile forms enter the circulation. Bunting's observation on bone marrow changes in experimental anemias produced by a circulating toxin—ricin—supports this view of the effects of bacterial toxins upon the hematopoietic system.

Hunter emphasizes the infectious origin of the "severest anemias," considering progressive pernicious anemia as a specific infective disease, while the other infective anemias are spoken of as "septic anemias" and intestinal infection anemias, the former being dependent upon oral, gastric and intestinal infections, the latter mainly due to parasitic disease.

The rapid recovery from severe anemia following the removal of nasal, tonsillar and dental infections, in which the organisms apparently possess marked hemolytic properties, strongly suggests the etiologic relation of those foci to the secondary anemia. This is particularly true of the anemia in patients with alveolar abscess associated with pyorrhea alveolaris.

Anaphylactic Reactions.—As previously stated in the consideration of the factors predisposing to infection and lessened localized resistance, the presence of persistent foci of infection apparently produces a particular sensitization of the body which results in manifestations of the anaphylactic type.

Bronchial asthma, urticaria and other vasomotor disturbances of the skin, gastro-intestinal symptoms, hypotension and arthropathy are disturbances that have been noted as the result of anaphylaxis and dependent upon the sensitization of the body to foreign protein.

The relation of anaphylaxis to bronchial asthma has been discussed by Vaughan, Meltzer, von Pirquet and others, and the etiologic relation of focalized bacteria to this type of foreign protein sensitization has been suggested by the work of Walker, Babcock and others. This apparent etiologic relation of focalized bacterial infection to foreign protein sensitization and the relation of such sensitization to bronchial asthma suggest that persistent foci of infection are frequently the underlying factors in this condition. Recently Oftedal has shown that streptococci isolated from the sputum in three cases of bronchial asthma elected the bronchial musculature in animals injected as the point of localization. The *Streptococcus viridans*, *Streptococcus hemolyticus* and a fusiform bacillus were found in the sputa. If this elective localization is common in bronchial asthma, it may be a factor in producing local sensitization of the bronchial tissues.

The improvement noted in some cases of asthma following the relief of nasal infection and mechanical irritation and the removal of infected tonsils strongly suggests the relation of these foci to tissue sensitization. Oftedal's observations may explain the failure in some cases evidently due to bacterial protein sensitization, on the ground that a focus of infection persists in the bronchial mucosa itself. While focal infection always should be sought, it must be borne in mind that sensitization to inspired and ingested non-bacterial foreign proteins is also a factor in bronchial asthma. The streptococcus, the staphylococcus, the *Micrococcus catarrhalis* and pleomorphic diphtheroid organisms are those most frequently found in asthma associated with sensitization to bacterial protein.

Neurasthenia.—Hypotension, general weakness and vasomotor irritability, noted not only as an evidence of anaphylaxis but in certain types of dysthyroidism, occur with such frequency in chronic focal infections that a diagnosis of neurasthenia requires a careful search for foci of infection.

DIAGNOSIS OF FOCAL INFECTIONS

The diagnosis of focal infection and the secondary effects arising therefrom depends upon: (1) an understanding of the pathology of the local and systemic diseases of proved bacterial origin; (2) a knowledge of the underlying principles of bacterial invasion, of the factors governing portal of entry, primary and secondary localization and the mechanism of symptom production due to body reaction; (3) a knowledge of the methods of precision in diagnosis, their limitations and the proper interpretation of the results obtained.

The pathology of those local and systemic diseases which have been discussed from the standpoint of their relation to focalized infection, is described in detail in chapters devoted to those diseases. The factors governing the incidence of bacterial invasion and primary focalization, of the dissemination of bacteria throughout the body, of secondary locali-

zation due to lack of resistance of tissue and to specific tissue affinity of bacteria and of local and general symptom production, have been discussed in this chapter. It is, therefore, necessary at this time to consider the methods employed to determine the location of foci of infection and their etiologic relation to a given local or general disease.

The detection of acute focal infections is not usually difficult, because of the objective and subjective symptoms of localized inflammation. The relation of such foci of infection to coincident systemic reactions, however, is often overlooked due to the tendency of clinicians to consider disease from the standpoint of its end pathology rather than from the standpoint of its primary etiology. At the present time no one fails to recognize the etiologic relation of a specific urethritis to a gonococcal infectious arthritis, the latter being looked upon as a complication arising during the course of the former. Many, however, fail to recognize that an acute iritis, an acute cholecystitis, an acute pancreatitis, an acute appendicitis or an acute oöphoritis may be a complication of an acute nasal, tonsillar or dental infection. If this relation was more generally recognized the same precautions to prevent secondary complications in acute infections of the upper respiratory and upper digestive tracts would be employed, as those in the treatment of gonorrheal infections, and more widespread and stringent prophylaxis to prevent such infections would be instituted.

Frequently, however, acute localized and systemic infections arise secondary to latent chronic foci of infection giving no local symptoms and it is then necessary to follow the same definite routine in examination as employed in determining the primary focus in chronic disease. The type of bacterial infection often indicates the portal of entry and consequent point of primary focalization. The foci of acute streptococcal infections will usually be found in the upper respiratory and upper digestive tracts; those of gonococcal infection in the genito-urinary tract; those of *Bacillus coli communis* infection in the intestinal tract; those of *Bacillus tuberculosis* infection in the tonsils, the lymphatic system or the respiratory tract and those of the diphtheroid infections, nasal, tonsillar and lymphatic. Early in life the foci are more frequently tonsillar; later in life, dental.

The determination of latent, persistent, chronic foci of infection is sometimes difficult and depends upon a careful, exhaustive clinical examination of the patient, which in itself may suffice to suggest a correct diagnosis; but whenever possible special examinations should be employed for precision in diagnosis. Some of the methods of precision are available to most practitioners, such as the roentgenogram, while others are difficult and can be carried out only by expert observers, as, for example, the determination of specific forms of bacteria and their etiologic significance. In the absence of certain of the methods of precision sound clinical judgment based upon a knowledge of the principles involved will accomplish much.

In a careful examination of a patient with a suspected focus of infection the following methods are of value:

1. Clinical history.

2. Special examinations:

Nasal: Visual, transillumination, roentgenography, bacteriological.

Tonsillar: Visual, bacteriological.

Aural and mastoid: Visual, roentgenography, bacteriological.

Dental: Visual, electric current for vitality, roentgenography, bacteriological.

Lymphatic: Visual, palpation.

Gall-bladder: Palpation, roentgenography.

Appendix: Palpation.

Genito-urinary: Urethroscopic, cystoscopic, segregated catheterization, bacteriological.

Rectal: Proctoscopic, bacteriological.

3. Laboratory examinations:

Blood examinations:

(a) Hemoglobin and absolute and relative cellular content.

(b) Serum reaction—antigen-fixation.

Bacteriological examinations:

Sputum, discharge from nose, throat, urethra, vagina and uterus; infected material from the tonsils and teeth; exudates; infected tissue; feces; urine; blood.

Clinical History.—Repeated occurrence of nasal and throat infections, of acute suppurative sinusitis, of peritonsillitis, of otitis media, of mastoiditis, of acute lymphadenitis, of alveolar abscess, of any infection of the genito-urinary tract, of anal or sigmoid infections, is always significant as indicating portals of entry and possible chronic foci of infection. Careful inquiry into the dental history, as regards the devitalization of root canals and unerupted teeth, is of assistance in directing the attention toward possible foci. The history of jaundice as indicating an acute cholecystitis or the eliciting of the symptom-complex of appendicitis indicates the possibility of persistent secondary foci of infection which may be the primary cause of the systemic symptoms under observation. The history of various disturbances in metabolism, of neurasthenia and of chloranemia should always direct the attention of the clinician toward the possibility of the existence of a persistent feeding focus of infection, either primary or secondary. Repeated bronchial, lung or pleural infections indicate the probability of lymph-node infection. The history of such acute bacterial invasions as the acute exanthemata, pneumonia, typhoid fever and the puerperal infections, should be noted. All of these conditions indicate the incidence of bacterial invasion and the possible sequential focalization of infection.

The physical examination in cases of focal infection, aside from that necessary to determine the nature of the pathological lesions of the disease in question, and of its complications, should be directed toward the location of any localized infection either at or near a portal of entry or at some point of secondary focalization. As already pointed out, the

most frequent sites of primary focalization are: nasal, tonsillar, dental, aural, genito-urinary and rectal. Each tract must be examined with the careful technique of a specialist.

Special Examinations.—**NASAL.**—The presence of nasal deformities interfering with normal drainage such as septal deflection, septal spurs, hypertrophied turbinates, predispose to sinus infection and must be given consideration. Persistent sinus infection is the usual form of nasal foci. In the acute form it is usually, though not necessarily, suppurative, while in the chronic form it is usually non-suppurative in type, which adds greatly to the difficulty in diagnosis, since the absence of discharge is apt to lead to the conclusion of negative findings. The presence of hypertrophied granular middle turbinates, polypoid degeneration of the turbinates, or the protrusion of polyps into the nasal cavity from the middle meatus, or the closure of the middle meatus with a sticky exudate, indicates chronic sinus disease. Sinuses containing granulating tissue must be considered of the same importance as granulation tissue elsewhere, since the conditions in the sinuses are favorable to increased tension. It is, therefore, from the end products of chronic sinus disease that a focal infection must be diagnosed rather than by visual evidence of the disease within the cell. Roentgenography is of some assistance, but unfortunately shows clearly only those diseased cells containing pus. Occasionally a maxillary or ethmoid sinus filled with granulation tissue may give a distinct shadow, but the difficulty of interpreting slight variations in cell shadow because of the transposition of structures on the flat surface of the plate is evident, and therefore while positive findings in the roentgenogram are conclusive, negative findings do not exclude the accessory sinuses as locations of focal infection. Transillumination is also of value, but the same limitations apply to this method as to roentgenography. Enlargement of the deep cervical glands may indicate persistent nasal infection. While the lymphatic drainage of the nose is directly to the retropharyngeal glands, the ultimate drainage is to the deep descending cervical chain.

TONSILLAR.—The presence of hypertrophied tonsils does not in itself indicate disease, but follicular involvement, even when the material is of a cheesy character, indicates local disease. Liquid pus is positive proof of surface infection and usually indicates bacterial invasion and the formation of an abscess in the lymphoid tissue of the tonsil. Localized abscesses are frequently found between the tonsils and the pillars. Congested and granular anterior pillars usually indicate deep-seated tonsillar infection. The small fibroid imbedded tonsil, even though the surface is free from evidence of disease, must always be looked upon with suspicion. Those tonsils in which scar tissue formation has partially or wholly occluded the orifices of the crypts are particularly dangerous. Tenderness and enlargement of the superficial or deep cervical lymph-glands are important signs in determining the presence of chronic tonsillar infection. Enlargement of the lymphatic gland at the angle of the jaw is particularly suggestive. This lymph-node is spoken of as the "tonsillar gland."

AURAL AND MASTOID.—The determination of chronic middle ear or mastoid infection depends upon the history of the case, the results of visual examination, and the roentgenographic findings. In the absence of chronic suppuration, enlarged lymph-nodes in the posterior cervical chain are indicative of chronic infection in this area.

DENTAL.—The method of determining dental foci of infection should be a routine one. Eisen and Ivy recommend the following:

1. Clinical and visual examination to determine the presence of pyorrhea, ulcerations, suppurating sinuses, swellings, enlarged lymph-nodes.
2. Determination of the response of each tooth to the faradic current.
3. Roentgenologic examination of each devitalized tooth as determined by its electric response.

Dental roentgenograms are important in determining the condition of unerupted teeth, for such teeth, even in the absence of local symptoms, may be the seat of a chronic focus of infection. The important point in dental diagnosis is to look upon all teeth and their surrounding structures as possible foci of infection until proved to be otherwise. Roentgenograms are absolutely necessary in this form of diagnosis and it must be borne in mind that even this method may fail to show areas of infection producing serious secondary manifestations. This is particularly true of granulomata, it being sometimes difficult to select rays of the proper degree of penetration to differentiate the diseased from the healthy tissue. Dental interpretation is difficult and requires the judgment of clinical experience. Oral surgery has long been neglected for the development of prosthetic dentistry and clinicians should consider this fact before being influenced by the dental findings of those interested mainly in mechanical dentistry. While a great many teeth have been needlessly sacrificed because of overzealousness and inefficient methods of examination, since the relation of dental foci to systemic disease has been more fully appreciated, a more serious danger menaces the patient who depends for dental diagnosis upon the man who ignores the value of roentgenograms and steadfastly follows the clinical methods of the past. A frequent experience is to find apparently healthy teeth with dead and infected pulps which even the roentgenogram fails to show and which have only been suspected because of their lack of electrical response. In one case of advanced chronic infectious arthritis that came under our notice, the teeth were apparently healthy, but each one was found to be dead with a putrescent pulp from which a streptococcus of high degree of oxygen sensitiveness was isolated. As Moorehead states, the probability of dental foci must be given first consideration in all cases between twenty-five and sixty years of age. Enlargement and tenderness of the submaxillary lymph-glands are suggestive of dental infection.

GASTRO-INTESTINAL.—*Chronic cholecystitis and appendicitis as foci of*

infection bearing an etiologic relation are always difficult of definite determination. As already pointed out, the history is of great importance. The diagnosis depends mainly upon the clinical symptoms and the physical signs which are described in other chapters. Roentgenograms to determine chronic cholelithiasis or enlarged and distended gall-bladder are unsatisfactory except when special technic is followed. The percentage of cases in which gall-stones are observed is estimated differently by various investigators. George and Leonard consider that they have detected gall-stones in from 50 per cent. to 85 per cent. of the cases examined, but few roentgenologists would be willing to give so high an estimate.

GENITO-URINARY.—Foci of the prostate and seminal vesicles, either gonococcal or streptococcal, must be determined by manual and bacteriologic examination. Infections of the bladder, ureters and pelvis of the kidney are mainly determined by the refined methods of urine segmentation and bacteriologic examination. Infections of the vagina, uterus, and adnexa are determined by the ordinary gynecological examination, combined with special bacteriologic methods.

RECTAL AND SIGMOID.—Rectal and sigmoid infections require special bacteriologic examinations to determine their relation to systemic disease. The presence of infected hemorrhoids, sinuses, fistule, ulcers and abscess pockets must be determined or excluded in the examination for focal infections in any case. Proctoscopic examination is necessary for the detection of foci of infection in this region.

Laboratory Examinations.—**BLOOD.**—The blood picture is of value in determining the presence of foci of infection. In acute focalization there is usually a polymorphonuclear neutrophilic leukocytosis associated with erythrocytic destruction. In persistent focalization of the subacute and chronic types there is usually a low color index with a moderate decrease in the erythrocytic count. The total leukocytes are as a rule increased from 9,000 to 12,000 on an average. In the subacute type of infection the leukocytosis often reaches 20,000 even in the absence of noticeable suppuration. This picture of chloranemia and moderate leukocytosis in the absence of plainly demonstrable causes should suggest the presence of localized infection in the body. Frequently, however, well "walled-off" chronic foci of infection cause no change in the total numerical count of leukocytes. In such cases, as well as those exhibiting a moderate leukocytosis, the determination of the actual number and percentage of the various forms of leukocytes in the circulating blood is of value. Importance is attached to the lymphocyte count, since chronic foci of infection produce a more or less constant irritation of the lymphoid tissue. Dependent upon the strength and type of the endotoxin, there is either stimulation or destruction of lymphocyte development. The differential count, therefore, is of importance.

Our clinical observations, supported by the laboratory findings of Bunting (verbal communication), in chronic non-suppurating nasal

foci of infection due to the streptococcus-pneumococcus group are to the effect that the toxin usually stimulates the lymphoid tissue so that an absolute and relative lymphocytosis occurs, in some cases being as high as 84 per cent., even though the total number of leukocytes may be normal. There is a moderate increase in eosinophils and basophils above the normal with a moderately high large mononuclear and transitional count. When the focus of infection produces an acute adenitis, the toxin has a destructive action upon the lymphocytes and the blood picture is similar to that found in the early stages of Hodgkins' disease, which is described below.

In chronic foci of infection due to the diphtheroid organisms, with secondary lymph gland changes (Hodgkins' disease), Bunting describes the blood picture in two stages. In the early stage there is a beginning lymphocyte destruction and the blood picture is not pathognomonic, as any acute infection may produce such a lymphotoxic substance. The total number of leukocytes is usually under 10,000. The lymphocytes are relatively low and continue to decrease in successive counts, falling as low as 15 per cent. There is a moderate eosinophilia in the average case which becomes extreme at times, rising to 60 per cent. in some cases. There is an early basophilia which diminishes as the disease progresses. There is a high percentage of transitionals and large mononuclears throughout this stage, reaching as high as 10 per cent. or above. The platelets are increased. The secondary picture Bunting considers pathognomonic. The total leukocytosis is from 15,000 to 100,000. There is an absolute and relative increase in the polymorphonuclear neutrophils up to 93 or 94 per cent. The lymphocytes in extreme cases drop as low as 1 per cent. The transitional and large mononuclear forms are higher than the lymphocytes reaching 8 to 10 per cent. The platelets are increased. Eosinophils and basophils are absent.

In adenitis without gland softening due to a focus of infection produced by the *Bacillus tuberculosis*, the total number of leukocytes may be normal or moderately diminished. There is a lymphocytosis, a low percentage or absence of eosinophils, a normal basophilia, a low percentage of transitionals and large mononuclear forms and an increase in platelets, with a decrease in the neutrophils. (See opposite page.)

With the exception of that seen in the secondary stages of Hodgkins' disease, these blood pictures are not absolute, but, in conjunction with the clinical findings, they have been found to be of confirmatory value in a great number of cases.

SERUM REACTIONS.—Serum reactions are of some value in determining the etiologic relation of an infecting agent to the local or systemic disturbance determined clinically. The Wassermann test is of value in confirming either the positive or negative clinical conclusions as to syphilitic infection. Complement-fixation tests for streptococci, gonococci and the other organisms isolated from suspected foci may be of assistance in the diagnosis of an etiologic focus, but are never absolute in value and must always be properly controlled.

DIFFERENTIAL LEUKOCYTE PICTURES IN CHRONIC NON SUPPURATING FOCAL INFECTIONS

	Chronic Streptococcal Nasal Infections	Chronic Diphtheroid Infection (Hodgkins' Disease)		Chronic Tuberculous Infections
		1st stage (Not Pathognomonic)	2nd stage (Pathognomonic)	
Total leukocyte count	Normal to 12,000.	Under 10,000	15,000 to 100,000	Normal or diminished
Lymphocytes	Increased 35% to 84%	Progressive decrease down to 15%.	Marked decrease down to 1% in extreme cases	Increased
Eosinophils	Increased.	Increase moderate to extreme 60%.	Absent	Low or absent
Basophils	Increased.	Early increase, then decrease.	Absent	Normal
Large mononuclears and transitionals	Increased	Marked increase, 10% or above	Increased 8% to 10%	Low
Platelets	Normal.	Increased	Increased	Increased
Neutrophils	Relative decrease.	Slight decrease	Absolute and relative increase; extreme cases to 94%	Decreased

BACTERIOLOGICAL.—Bacteriological examinations of infected material are of importance, since the laboratory evidence is sufficient to group certain diseases as being caused by one or the other forms of streptococci of varying degree of virulence and specific pathogenicity, differentiated mainly by their type of growth on blood agar and by their sensitiveness to oxygen. If, for example, a *Streptococcus viridans* is isolated from an abscess at the root of a tooth or in the parenchyma of a tonsil in a case of chronic infectious arthritis, or if a streptococcus exhibiting a faint zone of hemolysis is isolated from similar foci in a case of acute myositis, the determination of the etiologic focus is confirmed. The isolation of organisms with similar cultural reactions from both a focalized infection and the secondarily infected tissues of the blood is added confirmation that an etiologic focus has been determined. The detection of the *Bacillus tuberculosis*, the gonococcus or the diphtheroid organisms in suspected primary foci strengthens the clinical conclusions as to a secondary manifestation being tuberculous, gonococcal or one of the diseases belonging to Hodgkins' leukemia group (Bunting and Yates).

Therefore, the sputum, the discharges from the nose, throat, mouth, ear, rectum and genito-urinary tract should be examined. The blood should be cultured and when it is possible exudates or tissues from the area of secondary infection should be examined bacteriologically and microscopically. Cultures of the urine indicate the character of the causal infection and when compared with strains isolated from suspected foci of infection in the nose, tonsils or teeth, suggest the original source.

TREATMENT

The treatment of focal infections should be directed toward both the prevention and the cure of the primary bacterial invasion and focalization and its secondary results.

Prophylaxis.—From the foregoing discussion it is evident that the most important factor in the treatment of focal infections is the prevention of primary bacterial invasion. The development of preventive medicine has passed through the stages of sanitation and isolation and is now beginning to deal with the individual. The advances made in the control of small-pox by almost universal vaccination and the more recent evidence of the results of vaccination against typhoid fever show the value of treating the individual rather than alone attempting to destroy pathogenic bacteria.

The control of diphtheria by prophylactic doses of antitoxin, as well as the isolation of carriers, has had a marked effect upon the morbidity curve of this disease. Education and a betterment of moral and social conditions is assisting in the control of venereal diseases. Little progress, however, has been made in the control of the ordinary "colds" or "sore throats" which are treated lightly both by the physicians and the laity until a secondary complication arises which may be classified as a serious disease. Yet 50 per cent. of the morbidity of young adult life is due to acute localized reaction to this type of bacterial invasion of the upper respiratory and digestive tracts and almost 50 per cent. is due to the immediate or remote secondary effects of such invasion. The prevention of the so-called simple infections, therefore, should be made a matter of first importance. In the absence of any well-tested prophylactic measures, such as vaccines, for the protection against the common "cold" infection, it is necessary at present to protect the general community from the infected individual. The selfishness of streptococcic carriers and the laxity of the general practitioner and even of the public health official in directing their isolation result in the spread of an infection which leads to disastrous and widespread secondary results.

The treatment of acute bacterial invasion uncomplicated by secondary complications should receive rational attention. Not only should the resistance of the body be maintained or increased by absolute rest and sustaining nourishment, but the local infection should be treated not so much from the standpoint of destroying the bacteria by chemical antiseptics as by stimulating the local tissues to increased resistance and, wherever possible, by establishing normal drainage. Such treatment assists the body to overcome completely the bacterial invasion, thereby lessening the incidence of latent focalization.

Our experience in this regard is of interest. The establishment of medical supervision at the University of Wisconsin in 1910 permitted us to compare the results of the treatment of nasal and throat infections as local conditions with the results of the treatment of the systemic manifestations of such infections alone. With the former method the

average period of acute illness was 21½ days as compared with a period of 8½ days when the latter method was employed. The secondary complications, both mild and severe, such as inflammations of the eye and ear, pneumonia, acute rheumatic fever, etc., under the former method were only 12 per cent. as compared with 35 per cent. under the latter. Such treatment consists of evacuating wherever possible localized infections in the nose and throat. In the former, mild shrinkage of the middle turbinate with a **solution of adrenalin 1-25,000** or with a **solution of cocain hydrochlorid 0.25 per cent.** applied with pledgets results in the establishment of free drainage from the accessory cells through the middle meatus. This is followed by the use of a mild stimulant, such as a **solution of argyrol 10 per cent.** and a **vapor of menthol 1 per cent., camphor 1 per cent., in liquid albolene.** In tonsillar infections frequent hot normal saline gargles have been found to be more effectual than the more stringent and stimulating preparations.

The general prophylaxis of the nose, throat and teeth should be encouraged from childhood. One of the chief reasons of the low incidence of skin invasion as compared to that of the nose, throat and mouth is the frequent cleansing and the constant cellular desquamation. Similar methods of cleansing the mucous membranes of these cavities should be employed. Routine dental, nasal and pharyngeal supervision in our schools should be encouraged and the laity in general should be educated as to the necessity of these precautions. Detailed description of these methods may be found in chapters dealing with nasal and throat conditions.

Curative Treatment.—The treatment of determined foci of infection with or without local symptoms should be their immediate removal. To await until such foci produce secondary results is irrational. It is true that the incidence of primary focalization is much greater than the incidence of local or systemic diseases arising therefrom, but, if the latter are to be prevented, the former are to be eliminated as soon as detected. Radical procedures must be instituted with judgment. The wholesale removal of tonsils without definitely determining the presence of infection is unjustifiable. Radical operations for the correction of nasal deformities in children to improve aëration is unscientific unless mal-development of the upper maxillæ is considered and, if present, first corrected by orthodontic methods. The persistence of enlarged lymph-nodes following the removal of primary foci requires surgical interference if hygienic measures fail.

The treatment of acute focalized infections complicated by acute systemic diseases in many instances requires conservatism. Surgical procedures during the course of acute rheumatic fever, acute chorea, puerperal sepsis, acute endocarditis or acute pericarditis not only have no effect upon the course of the disease, but are apt to do harm by producing an overwhelming bacteriemia. Prophylactic measures in the treatment of the nose and throat are always indicated. In those cases secondary to an acute nasal infection, the maintenance of continued nasal aëration and drainage by the local treatment just described is a

rational procedure. The removal of persistent foci in such cases should occur *ad interim*.

In acute nephritis, erythema nodosum, gastric and duodenal ulcer, acute myositis, acute infections of the nervous system, the immediate removal of the etiologic focus is indicated when the general condition of the patient permits.

In the chronic diseases, the chronic focus or foci should be removed radically as soon as detected. It would be just as rational to treat the metastases of carcinoma without removal of the primary growth as it is to treat a chronic cholecystitis or chronic infectious arthritis without removing the primary source of infection.

Therapeutic measures are not confined to the removal of foci of infection, however, for the secondary infections do not disappear immediately with the removal of the feeding focus of infection. In the case of chronic infectious arthritis, for example, the periarticular tissues have been invaded by the bacteria of low virulence which have produced certain proliferative changes, have become focalized at that point and have developed definite elective affinity for joint tissues acting as a constant menace for the production of progressive, secondary involvement of other joints. The elimination of this persistent joint infection must be through the natural defenses of the body. Therefore, all of those measures tending to increase bodily resistance are to be employed with the same careful application to the individual as was the custom of clinicians prior to the knowledge of the underlying bacterial etiology of these conditions.

The first and fundamental principle in the treatment of focal infections is the treatment of the patient. There are always two factors involved in an infectious disease, the condition of the host and the species, virulence, number and special pathogenicity of the infecting agent. To ignore the former and deal only with the latter results in disappointment due to the failure to relieve the patient. To remove infected tonsils in a case of chronic gastric ulcer without treating the local gastric condition and the secondary results of disturbed metabolism is as irrational as to employ surgical and medical measures for the relief of the ulcer without removing the primary infecting cause.

It is not always possible to remove the primary focus radically. The strikingly beneficial results obtained following the removal of infected tonsils and the extraction of abscessed teeth are not experienced when dealing with chronically infected accessory sinuses or mastoids, since it is not always possible to remove all of the infected tissue. In such foci the principle is to establish freer drainage in the hope that the relief of tension and the consequent upbuilding of the resistance of the patient may bring about regeneration of tissue with elimination of infection. Too often, however, do we find the remnants of infected granulation tissue remaining in the cell cavities awaiting only the conditions bringing about increased tension, secondary to interference with drainage or acute infection to cause recurrent bacterial invasion.

The use of antibacterial sera, autogenous vaccines and non-specific

proteins in the treatment of acute and chronic infectious diseases is discussed in detail elsewhere. The value of such measures in the attempt to eradicate the primary etiologic foci of infection is irrational. Their employment in the treatment of the secondary manifestations resulting from such foci should be instituted with judgment only when the primary focus has been removed, since the danger of increased sensitization of tissues may lead to further bacterial invasion.

The hygienic and special therapeutic measures employed in the various acute and chronic diseases are discussed in detail in those chapters devoted to these diseases. In discussing such diseases from the standpoint of focal infections, it is not the purpose of the author to belittle the methods of treatment advised, but rather to emphasize them. But at the same time it is desirable, in applying such therapeutic measures, to keep in mind the importance of the primary etiology of these diseases and the mechanism of secondary infection, rather than to consider alone the end pathological changes.

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CHAPTER IX

ORAL SEPSIS

By H. B. ANDERSON, M.D.

Definition, p. 377—Historical summary, p. 378—Etiology, p. 381—Pathology, p. 386—Examination of the mouth, p. 391—X-ray examination, p. 394—Relation of oral sepsis to systemic disease, p. 396—Diagnosis, p. 411—Prognosis, p. 413—Treatment, p. 413—Oral prophylaxis, p. 413—Extraction of teeth, p. 414—The surgeon and oral infections, p. 415—Insurance and oral sepsis, p. 416.

Definition.—The term *oral sepsis* was introduced by William Hunter, in 1900, and is now commonly used by clinicians to designate the systemic effects of suppurative or infective dento-alveolitis. It is an infection, usually by streptococci, of the pulp, pericemental membrane, gums, alveolar sockets of the teeth, and often of the adjacent tissues of the mouth, tonsils, pharynx, sinuses and lymph-nodes.

Mouth infection is a broader term, including not only the above, but simple dento-alveolitis, the earlier or more limited manifestations of dental infection, without systemic symptoms, as well as the oral manifestations of the specific infections of tuberculosis, syphilis, etc.

Mouth infection is the commonest of all human diseases and in the vast majority of cases has its origin about the gums and teeth. Systematic investigations of the mouths of large numbers of people in different parts of the civilized world have shown that practically all adults and a majority of children have more or less oral infection. The incidence of the disease has increased with the spread of civilization and the attendant changes in environment, dietary and general conditions of living.

The two ordinary local manifestations of oral infection are: (1) pyorrhœa alveolaris,* which begins as a gingivitis and extends alongside the teeth, involving the pericemental membrane and alveolar sockets, accompanied by discharge of pus, recession of the gums and loosening of the teeth; and (2) periapical (alveolar) abscess, which usually follows infection of the pulp exposed by dental caries, with extension of the process through the apical foramen to the periapical tissues.

Pyorrhœa alveolaris is the less important from the standpoint of systemic disease, as the condition is more readily recognized, and

* The term "pyorrhœa alveolaris" is used throughout this article, being the one most familiar to the medical profession, though "periodontoclasia," or "dental periclasia," meaning a breaking down of the tissue around the tooth, proposed by A. J. McDonagh, of Toronto, has been adopted by the American Academy of Periodontology as more accurately descriptive of the condition.

since the pus usually does not accumulate under pressure efficient drainage—especially in the upper jaw—is more readily obtained.

Historical Summary.—Diseases of the teeth have been common in all ages and are referred to by the earliest writers on medicine. Examination of the teeth of prehistoric skeletons shows signs of caries, though less frequently than among civilized people. Dental diseases often being painful, sufferers in ancient times sought relief through the crude remedies employed by the practitioners of sacerdotal or popular medicine. The Papyrus Ebers (1550 B.C.) refers to dental and gingival diseases and the means for their relief employed by the ancient Egyptians. Extraction or other surgical procedures are not dealt with, though many authorities believe, from the study of mummies, that gold fillings and artificial teeth were in use at an early date.

Hebrew writers make no reference to dental diseases, the inference being that they were less common among this ancient people. The importance in which the teeth were held by the Hebrews, however, is suggested by the coördinate phrases, "eye for eye," "tooth for tooth," "hand for hand," "foot for foot" (Exodus, xxi, 24).

Researches into the early history of the Babylonians, Phenecians, Chinese and the inhabitants of India show that much attention was given by them to the care of the teeth.

From the earliest times, until the eighteenth century, the study of dental diseases and their treatment developed as a part of general medicine. While undoubtedly there were individuals especially skilled in extraction and the use of mechanical appliances, these did not form a distinct profession.

Hippocrates (460 B.C.) and other Greek physicians, and especially the philosopher Aristotle (384 B.C.) discuss diseases of the teeth and mouth with considerable detail, the history of dentistry showing the influence of their teachings for many centuries. Hippocrates mentions that abscess of the ear and necrosis of the jaw may be due to disease of the teeth, and discusses the symptoms arising from dentition and their significance. He advises upon the necessity for rinsing the mouth after meals, and in case of toothache, if the tooth is decayed and loose, that it be extracted.

Even before the foundation of Rome, knowledge of dental diseases and their treatment had made considerable progress among the Etruscans, who resorted to extraction and also used a form of bridgework to support artificial teeth.

The dental art was introduced among the Romans by the Greeks and Etruscans, and developed along similar lines, as indicated by the writings of Celsus, who, about 25 or 30 A.D., collated into eight books the medical knowledge of the period. He wrote extensively on diseases of the teeth, indicating a fairly advanced knowledge of them and their treatment.

Galen (131 A.D.), whose teaching exercised such a dominating influence on medical thought for centuries, gave considerable attention to diseases of the teeth, and distinguished pain, due to involvement of

their substance, from that caused by disease of the gums. In these early days extraction by forceps or the fingers was resorted to, but with much caution.

Rhazes (850 A.D.), Avicenna (950 A.D.), Abulcasis (1050 A.D.) and others of the Arabian school contributed little that was original, but followed closely the teaching of the Greek and Roman masters.

Little further progress was made until the time of the great anatomists of the sixteenth century—Vesalius (1514 A.D.), Fallopius (1523 A.D.) and Eustachius (1574 A.D.), whose studies corrected many errors which had been perpetuated for centuries, before human dissection was again resumed, after its practice by the Alexandrian school under Erasistratos (330 B.C.) and Herophilos (300 B.C.) had been discontinued.

Ambroise Paré (b. 1509), the celebrated French surgeon, contributed greatly to the progress of practical dentistry.

The founder of scientific dentistry was Pierre Fouchard (b. 1690) who practiced in Paris. By his writings he did much to establish dentistry as a specialty separate from general surgery, and since his time, medicine and dentistry gradually drifted apart and became recognized as distinct professions. Fouchard complained that "authors who have written on anatomy, surgical diseases and operations have only treated very imperfectly the part relating to maladies of the mouth and teeth. . . . This branch of the art having been but little cultivated, if not wholly abandoned by the most celebrated surgeons, their negligence has caused it to fall into the hands of persons without theory and without experience, who practice it in a haphazard fashion, guided neither by principles nor method."

The great English surgeon and pathologist, John Hunter (b. 1728), published two important works—a "Natural History of Diseases of the Teeth" (1771), and a "Practical Treatise on Diseases of the Teeth" (1778).

The importance of the teeth in mastication has undoubtedly led physicians and dentists in all ages, and even up to the present time, to consider dental diseases and dental loss too exclusively from the mechanical standpoint and that of cosmetic effect. It is not surprising that such should have been the case in the days before there was a knowledge of the relationship of microorganisms to disease.

The possible relationship of dental to systemic diseases, however, attracted the attention of acute clinical observers from time to time. Over a century ago Benjamin Rush reported the cure of a case of rheumatism of the hip-joint by extraction of a diseased tooth, and expressed the opinion that decayed teeth "were often the unsuspected cause of general and especially nervous diseases and . . . that our success in the treatment of chronic diseases would be very much promoted by directing inquiries into the state of the teeth in sick people and by advising their extraction in every case in which they were decayed." He makes the further statement, amply substantiated by recent investigations, "that it is not necessary that they be attended by

pain in order to produce disease," and quotes a number of contemporaries holding views similar to his own.

In the evolution of modern dentistry, America has taken a foremost place. In 1838, J. R. Spooner, of Montreal, introduced arsenic as a devitalizing agent for the pulp, a procedure which has since exercised an important, if not a beneficial, influence on dental practice. This treatment gave a great impetus to conservative dentistry in attempting to save many teeth which otherwise would have been extracted—a laudable purpose—but, carried to an extreme by mechanical ingenuity which overlooked the paramount importance of removing underlying infection, led to unforeseen ills from its practice.

John R. Riggs (b. 1811) gave special attention to the study of pyorrhea alveolaris, long known as "Riggs' disease," and introduced a new and more successful method for its treatment.

Horace Wells (b. 1815), by his discovery of nitrous oxid and ether anesthesia (1844 and 1846), will always be regarded as one of mankind's greatest benefactors.

W. D. Miller (b. 1853), an American who practiced in Berlin, where he became a Professor in the University, engaged in prolonged researches on diseases of the teeth and established the relationship of bacteria to dental caries. His scientific publications, about 100 in number, including his epoch-making work on "Die Microorganismen der Mundhöhle," in 1889, have made him the outstanding figure in scientific dentistry, and his researches paved the way for more recent investigations, which have thrown a flood of light on both dental and general diseases.

The observations and writings of William Hunter on oral sepsis in relation to pernicious anemia and other diseases must be credited with stimulating much of the recent interest in the question, and leading to many investigations of the greatest clinical importance. This work has been greatly facilitated by the routine use of the x-ray in dental diagnosis.

While one may appreciate the causes which led to the evolution of dentistry as a specialty apart from medicine, and the early advantages therefrom accruing to the practice of the art, its separation has been attended by unforeseen developments which have impeded the scientific progress of both. The study of general pathology has been neglected by the student of dentistry, and dental pathology by the student of medicine.

This illustrates the danger attendant on the study of the diseases of any organ or system without an intimate knowledge of their pathological and clinical interrelationships with other parts of the body. The present movement to bring dentistry back to its proper place as a branch of general medicine, the same as the eye, ear, nose and throat, therefore, has everything to commend it.

The dental profession, to their credit, have been foremost in warning of the dangers from oral infection. This, no doubt, is partly due to the fact that they are more familiar with the faults and deficiencies

of dental technic and, in their routine of work, have had the best opportunity for observing bad local results.

Etiology.—EXCITING CAUSE.—The mouth is the habitat of many forms of microörganism—pathogenic and non-pathogenic bacteria and ameba—some being constant and others temporary dwellers. As Miller points out, the oral cavity presents, in point of temperature, moisture, nutritive materials, etc., an almost perfect breeding place.

The poisonous nature of human saliva has been known since the time of Aristotle and Galen, though the first demonstration of microörganisms was reported by Van Leeuwenhoek, in 1683, who described five different kinds of "animalcula," which he found in material between the teeth.

A Dresden physician, Fincinus, is generally credited with being the first (1847) to attribute dental caries to the action of bacteria, though, according to Miller, he was antedated a few years by Erdl. In the following years a number of other investigators, including Leber, Miller, Underwood, Weil, Arkovy, Allen, Black and others, published articles in support of this view.

In 1881, Pasteur reported the discovery of the micrococcus of sputum septicemia, afterwards identified as the cause of lobar pneumonia and named the "pneumococcus."

The results of Miller's investigations, published in America under the title of "The Microörganisms of the Human Mouth" (1890), fully established the bacterial origin of dental caries, and pointed out the relationship of mouth infections to a number of systemic diseases, thus laying the scientific foundation on which has been built our present knowledge of the subject. He isolated 58 varieties of microörganisms from the mouth, many of which are pathogenic or may readily become so, and subsequent investigations have increased this number to over 100 (Figs. 1, 2, 3 and 4). According to Miller, caries is due to decalcification of the enamel by lactic acid elaborated during the carbohydrate fermentation of food, induced by mouth bacteria. A diet rich in carbohydrates, therefore, furnishes conditions favorable to dental decay, which opens the way for infection of the pulp by streptococci and other pathogenic organisms.

Many investigators have reported the absence of caries among meat-eating tribes, such as the Esquimaux, certain North American Indians, Lapps and Icelanders. W. A. Allen, in 1876, examined the mouths of 375 men, women and children among a tribe of Western Indians, without finding a trace of recession of the gums or abscess, and Pickerell reports a similar immunity among the Maori.

Bland Sutton and Miller have found carnivorous animals to be relatively free from caries.

The work of Schottmüller (1903), in differentiating various types of streptococci, paved the way for the later brilliant investigations of Rosenow on transmutations within the streptococcus-pneumococcus groups, and on selective tissue affinity, which have so illuminated many



FIG 1.—LONGITUDINAL SECTION OF DECAYED DENTINE, SHOWING INFECTION WITH ROD-AND-THREAD FORMS (After Miller)

Streptococcus mucosus, to the hemolytic streptococcus. Hundreds of different strains have been encountered, capable, under favorable cultural conditions or animal passage, of transmutation from one type of streptococcus to another, or into pneumococci. The mere presence of pathogenic microorganisms in the mouth does not mean active disease, since a healthy individual may not only harbor disease-producing germs, but may act as a carrier of infection to others.

Hopkins and Lang, discussing pathogenic streptococci, say: "We meet with strains which grow on healthy or even abraded mucous membranes without any tendency to invade or to produce a reaction in the host. We meet with others which set up generalized infections of the most severe type, and with all gradations

previously obscure problems of focal infection and the interrelationships of disease.

Important contributions to oral bacteriology have also been made by Sieberth, Goadby, Eyre, Rosenow, Hartzell and Henrici, Davis, Price, Gilmer, Moody and others.

In regard to the bacteria found in infected pulps, root canals, chronic periapical infections and abscesses, and pyorrheal pockets, as well as those responsible for the secondary local and systemic manifestations, there is general agreement that various strains of streptococci predominate. These streptococci vary in type from the ordinary non-hemolytic streptococcus, the *Streptococcus viridans* and



FIG. 2.—DECAYED DENTINE, SHOWING TOTAL LIQUEFACTION OF THE SUBSTANCE BY BACTERIA. (After Miller.)

between these two extremes."

Staphylococcus aureus, *Staphylococcus albus* and *Staphylococcus citreus*, pneumococci, *Bacillus influenza*, *Bacillus diphtheriae*, *Bacillus tuberculosis*, actinomyces, etc., are also found in the mouth at times, either alone or associated with streptococci, and may be the cause of mouth infection.

In 134 cases of gangrenous pulpitis, Sieberth, in 1900, found streptococci alone in 120 of the cases. Rosenow, in a study of 162 cases, has reported streptococci in 131 of the cases. Hartzell and Henrici found *Streptococcus viridans* constantly present in periodontal suppurative lesions. Animal experiments proved them to be of low virulence but capable of producing lesions in the heart, aorta, kidney and joints.

Cohen, in 62 cultures from 18 teeth that had been filled from six months to twenty years by sixteen different dentists, secured a growth of *Streptococcus viridans* in 60 of them, staphylococci in 16, associated with streptococci, and 1 each of *Bacillus coli* and *Bacillus acidophilus*.

Gilmer and Moody, in 16 cases of acute alveolar abscess, 18 cases of subacute or chronic abscess, and 8 diseased root-canals, found streptococci as the predominating organism in graded varieties from hemolytic streptococci with a wide hemolytic zone in acute cases, to *Streptococcus viridans* and *Streptococcus mucosus* in chronic cases.

Hartzell and Henrici, in the study of a series of acute dental abscesses, found the staphylococcus the active or-

ganism; while in the study of material taken from 250 infections of the chronic abscess or granulomatous type, the *Streptococcus viridans* was found to be the predominating organism.

In examination of the pus in cases of pyorrhea, Eyre and Payne found streptococcal types most

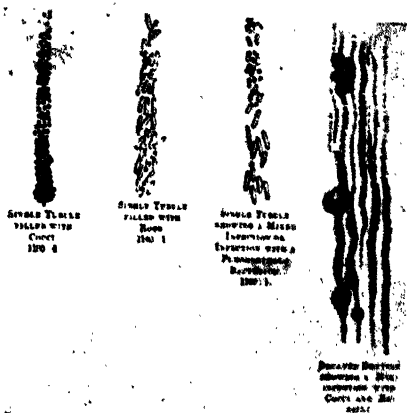


FIG. 3.—MULTIPLE PLATE. (After Miller.)

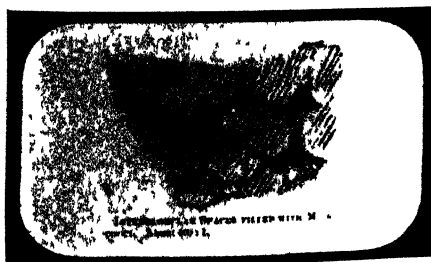


FIG. 4.—INTERLOBULAR SPACES FILLED WITH MICROCOCCI. (After Miller.)

frequently, at times associated with *Staphylococcus aureus* and *Micrococcus catarrhalis*.

While most authorities believe that pyorrhœa alveolaris is due to microorganisms, none of the organisms yet described as responsible for the disease has met with general acceptance. It is probable that different pyogenic organisms have a rôle in the production of the disease. The consensus of opinion of competent investigators assigns to the *Entamoeba buccalis* only a secondary rôle in association with other undetermined organisms.

Modes of Conveyance.—Mouth bacteria are introduced from the outside world especially by food and drink, inhalation, kissing, on foreign bodies, the fingers, infected tooth-brushes and by other obvious means.

PREDISPOSING CAUSES.—The bacterial content of the mouth is increased by all forms of uncleanness, lack of care in brushing the teeth and cleansing the mouth, accumulation of food around and between the teeth, by tartar or dental calculus, crowns, bridges, pivots. Ill-fitting or neglected dentures tend not only to harbor infection, but frequently to seal it in. Rough or poorly constructed mechanical appliances cause local irritation and thus predispose to infection.

Dead and carious teeth, old roots, detached gums and loose teeth, themselves the result of infection, furnish favorable local conditions for its continuance. According to Black, mechanical strain on the teeth—about 1,700 pounds pressure daily—is an important factor in predisposing to infection, a point well illustrated by the proneness to disease in teeth which serve as the abutments of bridges. Hartzell describes the piston action of this force transmitted through the tooth to a periapical abscess and pyorrheal pockets and its effect in forcing the infection into the blood and lymph streams.

Among important predisposing causes of oral sepsis may be mentioned:

(1) Poorly developed, soft, porous teeth or dental defects, as holes, cracks and fissures in the enamel (Miller).

(2) Enlarged tonsils, adenoids, nasal obstruction and other causes of mouth breathing; oral deformities, dental irregularities, crowding, and imperfect occlusion of the teeth.

(3) Neglect of the teeth during the primary dentition and of the mouths of children after nursing, feeding, during illness, in early disease of the gums, caries and toothache.

(4) Insufficient care of the mouths of adults during acute infections and prolonged illnesses which reduce the patient's systemic resistance.

(5) Constitutional conditions, as scurvy, rickets, syphilis, digestive diseases, tuberculosis, diabetes, Bright's disease, gout, anemia, pregnancy and lactation. Many of these act by producing an acid reaction in the saliva (Miller).

(6) Mercury, lead, iodids, inorganic acids, administered as medicines, gritty dentifrices, etc.



FIG. 5.—PERIAPICAL INFECTION ASSOCIATED WITH RETAINED INSTRUMENT.



FIG. 6.—PERIAPICAL INFECTION ASSOCIATED WITH CROWN, DEEP-SEATED CAVITY AND PIVOT TOOTH.



FIG. 7.—PERIAPICAL INFECTION ASSOCIATED WITH DEEP SEATED CAVITY.



FIG. 8.—PERIAPICAL INFECTION SURROUNDING VITAL TOOTH.
Septic tooth anterior to it.



FIG. 9.—PERIAPICAL ABSCESS OF VITAL TOOTH.



FIG. 10.—PERIAPICAL ABSCESS.
Palpable. Result of trauma.

(For the preparation of this series of plates, illustrating various types of dental infection, the author is indebted to Dr. H. W. Fox.)

(7) Excess of sugar and other carbohydrate foods.

(8) Trauma and infection of the gums, from tooth-picks, during dental treatment, from rough or ill-fitting mechanical appliances, the use of rubber dams, and other causes producing irritation or local injury to the tissues.

Pathology.—Mouth infection usually begins about the teeth, either after exposure of the pulp by caries, or as a gingivitis extending along-side of the tooth, and involving the pericemental membrane as in pyorrhœa alveolaris. Miller's researches show that caries is due to decalcification of the enamel and, afterwards of the softer dentine, by acids elaborated by lactic-acid-producing mouth bacteria.

Once the dental pulp is exposed it becomes infected by streptococci or other pathogenic organisms and if the process is not checked, it extends through the apical foramen and involves the pericemental membrane and adjacent bone (Figs. 6 and 7). The injury to the pulp by the infection, the pressure on the vessels by swelling in the non-elastic pulp cavity, and the cutting off of the blood supply through the apical foramen, lead to death of the pulp and thus the destruction of an important source of the tooth's nutrition. The process often proceeds to pus formation (alveolar abscess), which may make its way to the surface in various situations or remain as a chronic "blind" abscess. Hartzell believes that pulp infection, in the absence of caries, frequently occurs through the exposed gingivodental angle. He has a record of 150 teeth which were absolutely sound as far as the enamel was concerned, but the pulps of which had been destroyed by infection, and he quite often finds teeth, the pulps of which are undergoing profound inflammation without having been exposed to decay. In rare cases periapical abscess may be secondary to the systemic infection, especially if local injury or irritation has reduced the tissue resistance (Figs. 9 and 10).

If the pericemental membrane remains intact, it may be sufficient to nourish the tooth in which the pulp has been destroyed, but if it becomes much involved, by extension of the apical infection or by pyorrhœa alveolaris, the tooth dies and remains a septic foreign body in the alveolar socket. Under these circumstances extraction becomes necessary in order to remove the septic process.

If the condition is treated early, before the infection extends through the apical foramen, the dead or infected pulp cleared out, the cavity carefully disinfected and the root-canals properly filled, the septic process may possibly be eradicated and the tooth saved.

Experimental investigations by Weston A. Price, as to the efficiency of medicaments to sterilize the pulp cavity and canals, indicate that this is a much more difficult procedure than dentists have realized; such treatment frequently fails, and the present dental technic, he believes, will need to be completely changed.

The fate of the tooth depends upon preventing the extension of the



Fig. 11.



Fig. 12.



Fig. 13.



Fig. 14.

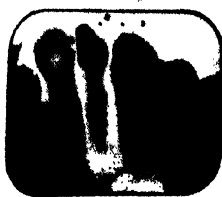


Fig. 15.

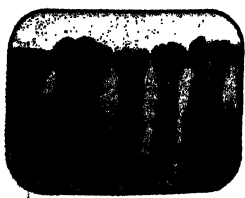


Fig. 16.



Fig. 17.

**FIGS. 11-17.—PERIAPICAL INFECTION ASSOCIATED WITH IMPROPER
ROOT-CANAL FILLING.**

infection through the apical foramen, the development of periapical abscess, and destruction of the pericemental membrane.

Degrees of periapical involvement, short of pus formation, may be compatible with healing, but, unfortunately, due to careless technic, the use of corrosive drugs, such as arsenic, or gas-producers, as hydrogen peroxid, creosote, or as the result of trauma, or failure to sterilize and properly fill the root-canals, abscess formation frequently occurs. If the tooth is vital, most dental authorities, while admitting the difficulty of the problem, believe that conservative treatment may be successful. Much depends upon the patient's general health.

Authorities generally emphasize the extreme importance of proper disinfection and filling of the root-canals in forestalling serious periapical infection. At all times a difficult and tedious procedure, it is especially so when the canals are small and tortuous (Figs. 11 to 17).

The bearing of root-canal technic on infection is well illustrated by A. D. Black's roentgenographic investigation of 600 cases, in which ten films were made in each case, which showed only 9 per cent. of abscess in teeth with good root-canal fillings, contrasted with 63 per cent. in teeth with poor root-canal fillings.

Much confusion has arisen from the common use of the term "devitalized," by dentists, to describe a tooth from which the pulp has been removed and thus rendered insensitive to pain; but, strictly speaking, if the pericemental membrane remains intact or has not been seriously involved, the tooth may still receive sufficient nourishment to maintain a degree of vitality so that a so-called devitalized tooth is not necessarily a "dead" tooth.

Dr. A. E. Webster differentiates a *pulpless* from a *dead* tooth and outlines the best procedure in each case, as follows:

"A pulpless tooth is one in which the vitality of the pulp has been lost. To determine the vitality or non-vitality of dental pulps, one must consider the history of the tooth, its color and translucency, presence or absence of tenderness of the pericemental membrane and response to changes of temperature or to electric current. Even with these cardinal signs and many others of less value it may almost be impossible to make a differential diagnosis.

"A pulpless tooth may remain in the mouth, performing its normal function for years, without the slightest injury to its owner.

"The value of a tooth is determined by the condition of its pericemental membrane. If the latter is normal, the tooth is never the source of systemic infection. While a pulpless tooth never has a normal pericemental membrane, it does not follow that it is a source of infection.

"A periapical infection can be cured without extraction, provided there is enough pericemental membrane to retain the tooth and make it useful. If one-quarter of a root, however, has lost its pericemental membrane, it is useless to apply any sort of treatment except extraction and curettement.

"A dead tooth, on the other hand, has not only lost the vitality of its pulp, but also that of the dentine, cementum and pericemental mem-

brane. The tooth being dead *in toto*, is to all intents and purposes a foreign substance, is porous, permeable to bacteria, and therefore extraction is always demanded.

"To differentiate a pulpless from a dead tooth, the history is of first importance. A tooth giving a history of several attacks of acute peri-dontitis, the root-canals of which have not been properly cleaned out and filled, which has lost its usefulness, changed its position in the ridge, is of a gray-greenish color, with the pericemental membrane more or less detached around the neck and has a local area of redness of the mucous membrane covering the root, is surely a dead tooth. A

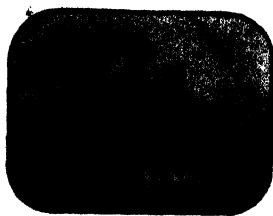


FIG. 18.



FIG. 19.



FIG. 20.



FIG. 21.

FIGS. 18-21.—RETAINED SEPTIC ROOTS.

skigram is of value in corroboration of the diagnosis, but is not essential."

Dead and pulpless teeth must always be recognized as potentially dangerous, the more so since periapical abscess may develop without pain or other evidence of its presence. Horder says: "Very few dentists are themselves alive to the fact that a dead tooth which is firmly held and which shows no suppuration may be the main factor in one or other of several disease processes"—an opinion with which experienced clinicians will agree. According to Rhein, the most insidious and dangerous type of infection is that around the root, with no pus formation and no sinus, known as a "dental granuloma."

Tovell made roentgenographic films in 281 of the author's series of cases, including in all 3,276 teeth. Of the previously treated teeth, 1,168, or 73 per cent., showed evidence of disease, either by definite peri-

ORAL SEPSIS



FIG 22

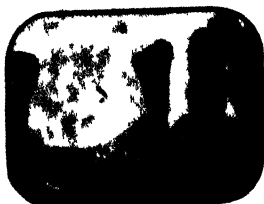


FIG 23

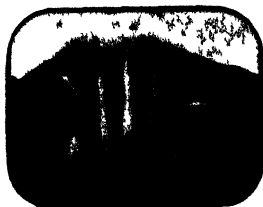


FIG 24



FIG 25



FIG 26

FIGS 22-26 —PYORRHOEA ALVEOLARIS

apical abscess or marked changes in the pericemental membrane Of the non treated teeth, 133 or 4 per cent., showed evidence of periapical involvement (exclusive of pyorrhœa alveolaris)

In the examination of films of 1 000 medical cases in office practice Duke found evidence of bone absorption in 81 per cent of non vital teeth Ulrich states that 70 per cent of artificially filled teeth are septic, and Leonard found 60 out of 100 cases In a mouth containing devitalized teeth—crowns bridges and pivots—the presumption, therefore, is greatly in favor rather than against infection

Practically all roots and snags left after decay or extraction are septic Duke's roentgenographic investigations showed evidence of infection in 93 per cent. and relatively marked in 57 per cent. (Figs. 18 to 21).

Extension of infection alongside the teeth, separation of the gums

destruction of the pericemental membrane and involvement of the tooth socket from above, as in pyorrhœa alveolaris, is a more obvious process of dental disease (Figs. 22 to 26).

The rarity of finding an adult mouth free from all evidence of infection is emphasized by many investigators. Gilmer has stated that 75 per cent. of adults have chronic infection involving the maxillary bones.

In A. D. Black's series of 600 cases, he found evidence of infection about the teeth in 50 per cent. of those between 20 and 24 years of age; 64 per cent. in those from 25 to 29 years; 88 per cent. in those between 30 and 39 years; 90 per cent. in those between 40 and 49 years and 98 per cent. in those 50 years or over, indicating the increasing infection with advancing years. This is counterbalanced, however, by extractions though all persons with extensive or complete extraction have obviously at some time suffered from serious mouth infection. Abscesses may be found around unerupted teeth (Fig. 57).

Serious oral infection certainly has increased with the development of mechanical dentistry, where the teeth are buttressed and infection is sealed in. Chronic periapical abscesses are dangerous, as they are accompanied by little reactive inflammation to wall off the infection, the pus accumulates under tension and, according to Rosenow and Billings, the conditions as to oxygen tension and other factors are favorable for transmutation of the streptococcus to the types capable of infection, and the acquirement of a selective affinity by which distant organs or tissues are involved.

To indicate the extent of diseased tissue in oral sepsis, Hartzell has stated that if each of the 32 alveoli and 30 interdental spaces through which infection in the adult may occur had pyorrheal involvement to the depth of $\frac{1}{4}$ inch, it would represent an ulcerating surface of $7\frac{1}{2}$ square inches.

Examination of the Mouth.—This is of the greatest importance and should be part of the routine investigation of every patient, and especially in all chronic diseases. In the mouth of an individual containing pulpless teeth, crowns, bridges, pivot teeth and fillings, as before stated, experience bears out the *presumption of infection* rather than its absence (Figs. 27-44).

The degree of sepsis around dentures and other mechanical contrivances, carious teeth and old roots, especially where dental work has been badly done or neglected, is at times appalling to the examiner. Many patients have absolutely no painful local symptoms even with extensive oral disease and often few obvious signs of trouble. Among the wealthy and well-to-do who have visited the dentist most faithfully and have had the most expensive mechanical dentistry carried out, the degree of oral infection, while at times less evident on superficial examination, is pathologically often more serious than in the neglected mouths of the poor. Every tooth, therefore, the surrounding gums, the mucous membrane of the throat, the tonsils and cervical



FIG. 27.—INFECTION OF ABUTMENT.



FIG. 28.

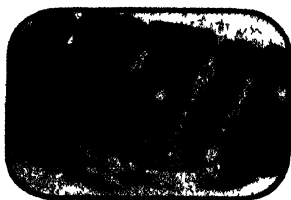


FIG. 29.



FIG. 30.

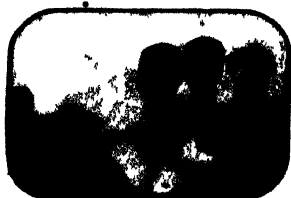


FIG. 31



FIG. 32



FIG. 33



FIG. 34.



FIG. 35.

FIGS. 28-35.—PERIAPICAL INFECTION ASSOCIATED WITH CROWNED TEETH.

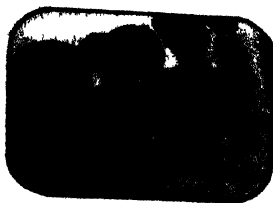


Fig 36



FIG. 37



FIG 38



FIG. 39



FIG 40



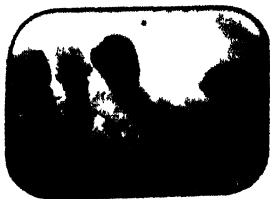
FIG 41



FIG 42



FIG. 43.



lymph-nodes, should be examined in a good light, by inspection and palpation.

A characteristic sweetish, offensive breath, foul tongue, swelling and purplish-red discoloration of the gums; thickening of the alveoli around certain teeth beyond the general contour, small fistulous openings, scars, or tags in the mucous membrane over the apices of the alveoli; dark or carious teeth; the escape of blood and pus on pressure, separation or recession of the gums, local irritation from ill-fitting dentures, crowns, bridges or pivots; whitening and thickening of the mucous membrane of the mouth; calculus deposits; miliary enlargement of the submucous lymph follicles, small ulcers; enlargement or tenderness of the submaxillary lymph-nodes, at times of the thyroid gland; stomatitis, tonsillitis, pharyngitis and hypersecretion of the throat, are conditions worthy of attention in directing further examination. Every doubtful tooth should be tested for its vitality by heat and cold, as also by the faradic current.

When the physician discovers evidence of trouble or has reason to suspect it, the patient should be referred to a competent dentist for more complete examination. The final responsibility for the patient's general health, however, rests with the physician and he must be satisfied only with the most complete and trustworthy investigation.

Experience teaches that in a mouth with fillings, crowns, bridges and pivots, a superficial appearance of health does not warrant the exclusion of even the most serious periapical infection. Therefore in all such cases roentgenographic examination should be made and repeated from time to time, especially if evidence of systemic disease develops.

X-RAY EXAMINATION.—The routine use of the x-ray in the diagnosis of periapical abscesses or granulomata, cysts, pyorrhea pockets, osteitis, retained roots, pulp stones, unerupted teeth, filling of root-canals and sinus disease, is of great value. It is also of use in directing dental treatment and in following the results obtained.

The making and interpretation of roentgenographic films requires skill and experience; self-confidence and dogmatism characterize the tyro, not the trained observer.

It should be borne in mind that the x-ray depends for its results upon variations in density from the normal, due to the processes of disease, so that in the early stages of infection or where there is slight tissue change or local reaction, the results of infection may not be demonstrable by this means.

The x-ray by itself cannot distinguish an active from a quiescent lesion or rarefaction due to drugs, nor an apical granuloma from an abscess. MacKee says, "An apical shadow simply signifies decalcification from any cause." In general, it shows the *minimum* rather than the *maximum* amount of trouble.

To minimize errors, it is often necessary to take the films at different angles. The varying thickness of the alveolar processes, the overhanging antrum and the presence of the mental foramen, present technical difficulties which must be borne in mind.

In the presence of naked-eye evidence of infection, negative x-ray findings do not warrant, as often happens, our placing a higher value on the roentgenologist's observations than on those of the clinician. Zentler has isolated the *Streptococcus viridans* from the apices of teeth which showed no evidence of bone absorption by the x-ray, and not infrequently streptococci may be cultivated from extracted roots where the roentgenograph showed little or no evidence of trouble. Absence of abnormal roentgenographic areas, therefore, does not necessarily mean that the tissues are healthy.

In arriving at a diagnosis, the opinions of the physician, the dentist



FIG. 45.

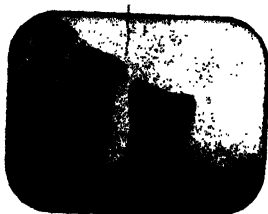


FIG. 46.



FIG. 47.

FIGS. 45-47.—MARKED PERIAPICAL INFECTION ASSOCIATED WITH SYSTEMIC SYMPTOMS WITHOUT EXTERNAL EVIDENCE OF DISEASE ON LOCAL INSPECTION

and the roentgenologist should each be given due consideration. As Eisen and Ivy state, we are never warranted on roentgenographic examination alone in hazarding a clinical or pathological diagnosis. Merritt also says that serious secondary infections may result from a non-vital tooth which roentgenologically appears to be normal, and that to attempt to make a diagnosis or to outline treatment based on such examination is never wise, for not only is it likely to be wrong, but it may seriously mislead the clinician.

Neither does the size of an abnormal area bear any definite relation to its pathological importance. In individual cases, much difficulty arises in the interpretation of the significance of slight degrees of rarefaction of bone or thickening of the pericemental membrane.

The importance of minor degrees of infection, therefore, must not

be overlooked. Even a single infected tooth in a susceptible individual may suffice to produce general symptoms, or to prolong them, if already present. This applies especially to doubtful teeth, utilized by the dentist, for mechanical reasons, as the abutments of bridges or to hold artificial dentures in position. The author's experience leads him to believe that pivot teeth are especially liable to be the seat of infection, even more serious than is indicated by roentgenographic examination.

Moorehead points out that partially healed and residual infections may be as dangerous as before treatment.

Relation of Oral Sepsis to Systemic Disease.—While individual physicians in the past have directed attention to infection of the gums and teeth as a cause of systemic disease, the majority of physicians and dentists have failed to recognize its importance. Miller, in 1890, wrote:

"It is a well-known fact that the inflammatory processes in the tooth-pulp, pericementum and gums, brought about by a diseased condition of the human teeth, lead not only to obstinate neuralgias, but also to severe diseases of the eye and ear, to eruptions of the skin, spasm of the muscles, etc.

"Cases of spasm of the facial muscles, lockjaw, convulsions, spasm and paralysis of the ciliary and other muscles of the eye, strabismus, ptosis, lagophthalmus, epiphora, ectropion, asthenopy, amaurosis and amblyopia, mydriasis, myosis, glaucoma, cataract, keratitis, retinitis, conjunctivitis, panophthalmitis, otitis, thrombosis of the sinuses of the brain, eczema of the face, indigestion, nervousness, epileptic attacks, paralysis, etc., proceeding from decayed teeth, come to our notice, many of them repeatedly, in dental and medical literature. . . . The custom of many physicians to disregard dental diseases altogether as a factor in pathology, is as unjust to their patients as it is discreditable to their profession, and no physician can afford to be without a thorough knowledge of the pathological processes occurring in the human mouth and their relation to general diseases."

Especially since the publication of William Hunter's work, in 1900, has the subject received the attention of many investigators in both medical and dental professions. Literature has multiplied and the present tendency is to go to extremes in attributing, often on insufficient evidence, all sorts of ills to this cause.

Oral infection of varying degrees is so common, and therefore of necessity frequently associated with whatever diseases the patient suffers, that its etiological relationship in a given case requires the most critical investigation, if we are to escape the pitfalls which beset *post hoc* reasoning.

Sufficient reliable data, both clinical and experimental, have accumulated, however, to show that focal infection in the mouth is frequently the cause of general disease. Further investigation and clinical experience are necessary before entirely trustworthy conclusions are reached, yet there can be no doubt of its practical importance to the practitioner of medicine and dentistry. It is not too much to say that inves-

tigations during the last ten years have revolutionized dental technic, and have opened up many new lines in the diagnosis and treatment of disease.

In many instances, mouth infection may exist for years without definite evidence of ill health, though careful inquiry and examination will discover in some, who consider themselves in good health, various complaints such as rheumatic pains, slight grating in certain joints, neuritis, myositis, tonsillitis, lumbago, digestive ailments, nervousness and other danger signals of disease, awaiting the morbid opportunity when resistance is lowered to develop more serious symptoms.

The most complete clinical and experimental investigations of the relationship of dental to systemic infection are those dealing with cardiovascular, renal, arthritic and muscular lesions, certain diseases of the nervous system, the eye, alimentary tract and gall-bladder. The rela-



FIGS. 48 AND 49.—EXTENSIVE PYORRHEAL AND APICAL INFECTION OF LONG STANDING IN MALE PATIENT, AGED 63, WITH NO SYSTEMIC SYMPTOMS EXCEPT RECENT LUMBAGO.

tionship of oral sepsis to skin lesions is suggested largely on clinical observations of their association, and improvement after dental treatment.

Chronic oral infections are usually of a low grade of virulence, often sealed in, and extend over a long period. To study the evolution of such infections and to appreciate their various clinical manifestations, they must be followed for a long time, the same as syphilis and tuberculosis. Private practice, therefore, offers a better opportunity for their study than hospital practice. A careful clinical history in each case, with special reference to previous ailments or disease, is of the greatest importance. It is characteristic of oral infections that, as a rule, they do not produce a single systemic lesion, but often a group of allied conditions, usually not all manifested at one time, but which appear as phases of a long period of ill health. This tendency to produce multiple lesion is also shown experimentally. Moody, by injection of young rabbits with dilute apical pus, in 8-13 days found streptococci in the myocardium, suppurative arthritis, and hemorrhages in the renal subcapsular tissues, stomach walls and maxillary muscles. Rosenow, Hartzell and others have reported similar results. Potter enumerates 31 common clinical manifestations in the vicious circle established by

oral sepsis, and Osborne also emphasizes the tendency to produce a multiplicity of diseased conditions. This point is well illustrated in notes selected from the histories of the writer's series of over 450 cases in private practice, in which certain characteristic disease groups repeatedly recur, of which the following is an instructive example:

CASE I.—Mrs. P.: age, 30 years; seen on Dec. 1, 1916. Patient complained of neuralgic headaches, mostly on left side; has suffered from bad colds; numbness and heaviness on right side of body; attacks of urticaria; rheumatism; sciatica; was depressed and nervous. At time of examination patient was pale, hemoglobin 70 per cent.; skin dry; tongue very coated; breath offensive; had chronic pharyngitis and tonsillitis; teeth very septic, though she had visited dentist regularly and on superficial examination mouth appeared well kept. Dr. McDonagh made x-ray examination and reported left upper second bicuspid, left upper cuspid, lateral and central, all septic, and left first bicuspid doubtful. There were sinuses opposite the left upper lateral and the posterior molars, through which pus could be expressed by pressing on the left side of the roof of the mouth internally, and on the left side of the nose about the angle of the eye externally. On extracting the teeth, the antra on both sides were opened up and discharged pus; x-ray examination also showed extensive necrosis of the alveolus. The antra eventually closed up satisfactorily. During early part of treatment, after extraction of many teeth, patient's health deteriorated; she lost weight, became very weak, scarcely able to walk, but began gradually to regain her health. Wassermann was negative.

March, 1918.—Weight, 117 pounds; hemoglobin 95 per cent.; patient has been sleeping fairly well; complained of tiring out readily. Considerable involvement of bone still remained, but it was deemed best to temporize, as she was improving. While on a holiday in Atlantic City she became very nervous, did not sleep. On her return to Toronto, an examination was made on May 1, 1918, with the following findings: her weight was 112 pounds; she complained of numbness in the whole of the right side of the body; jerking and twitching; eyes were bright and slightly prominent; she had thyroid enlargement, especially involving the middle lobe.

May 11, 1918.—Patient feeling better; pulse still 120; very nervous; marked tremor and thyroid enlargement. Tonsils small, buried; pus readily expressed from crypts. *Streptococcus viridans* in cultures.

June 18, 1918.—Tonsils were removed and, in October, thyroidectomy was performed. Since these operations, the patient has greatly improved, though there is still evidence of infection in the upper maxillary bone. During her prolonged illness the following conditions were manifested: *oral sepsis, tonsillitis, rheumatism, sciatica, double antral suppuration, eczema, urticaria, nervous exhaustion, exophthalmic goiter, anemia* (70 per cent. hemoglobin), *albuminuria* (slight) (Figs. 50 to 54).

The increase of certain diseases, coincident with the development of mechanical dentistry, has been sufficiently noticeable to attract the at-

tention of even the laity, and opens an important field for investigation as to the responsibility of oral infection in this connection. According to Rhein, statistics show that the death rate in the United States in infancy, adolescence and early middle life has been steadily decreasing, whereas at older ages, diseases of the heart, blood-vessels, kidneys, etc., have practically doubled in the past 30 years, or during the period since conservative treatment of the dental pulp has replaced extraction. In Great Britain, on the other hand, where this treatment



FIGS. 50-54.—EXTENSIVE ORAL INFECTION, WHICH PRODUCED MULTIPLICITY OF SYSTEMIC DISEASES. (Illustrating Case I.)

has never been extensively used, the mortality in advanced years has shown a slight decrease.

Focal infection in the mouth is a frequent cause of enlargement of the cervical and mediastinal lymph-nodes, especially in children. Severe and even fatal glandular fever may occur. Bacteriological examination and animal inoculations show that infection by *Bacillus tuberculosis* and streptococci is common. Pus formation is not infrequent. The glandular condition may clear up after removal of the primary focus, but at times it persists as a focus for secondary infection (Billings).

Odenthal found glandular swellings in 99 per cent. of children with marked oral infection (abscessed teeth) compared with 49 per cent. in those with sound teeth (Fig. 55).

BLOOD.—William Hunter, in his work on the "Severest Anemias," advanced the theory that anemia of the pernicious type was infective in origin and frequently due to oral sepsis. Chronic focal infections in

the gall-bladder, heart and elsewhere are not infrequently associated with severe grades of anemia. While Hunter's views have not met with general acceptance, the importance of infection as a cause of anemia is receiving more attention on the part of clinicians. In general, the improvement in severe types of anemia after the removal of focal infection in the mouth, has not been sufficiently pronounced to strengthen Hunter's views, though it must be recognized that the failure to improve may be due to persistence of secondary foci, or to injury done before the primary focus was eradicated. Potter, McNeill and Bradbury in the investigation of 25 cases of oral sepsis, did not find anemia a characteristic feature. In the examination of the blood of 162 cases Logan found pronounced anemia only once and moderate anemia infrequently. Leukopenia was more constant than leukocytosis in pyorrhea alveolaris, whereas leukocytosis was present in 47 out of 52 cases of periapical infections without discharging sinuses. In the writer's



FIG. 55.—INFECTION OF DECIDUOUS TOOTH, SECONDARY INFECTION OF SUBMAXILLARY LYMPH NODES.

series of 450 cases, extreme degrees of anemia have not frequently been met with, though a moderate reduction of hemoglobin—from 10–30 per cent.—has been a common observation, being noted in 17 per cent., an experience in keeping with that of most other clinical observers.

RESPIRATORY SYSTEM.—An alveolar abscess may rupture into the nasal cavities or antra, or oral infection extend to the ethmoidal or sphenoidal cells or the frontal sinuses: rhinitis, nasopharyngitis, and tonsillitis are common, often accompanied by a sensation of dryness, redness and hypersecretion of the throat; retropharyngeal abscess may occur. In the author's series of 450 cases definite tonsillar infection was noted very frequently, and laryngitis, tracheitis and bronchitis may result by extension downwards of the throat infection.

In cultures on blood-agar from the tonsils in 209 of the author's cases, R. W. Mann found streptococci in 138 (non-hemolytic in 83 hemolytic in 5, viridans in 34, type not stated in 16); *Staphylococcus aureus* in 20; and *Staphylococcus albus* in 89; *Staphylococcus aureus* alone in 6; associated with other organisms in 14; *Staphylococcus albus* alone in 49; associated with other organisms in 89. The tonsils were often atrophic and concealed, at times mere tags or stumps, left after

operation; but on pressure, pus would exude from the crypts or peritonsillar tissue. Frequently the patient complained of no discomfort, and in a superficial examination of the throat the trouble might readily be overlooked. In many cases, where previous clipping of the tonsils had been done, the resulting scar tissue had occluded the openings of the crypts so that pus was sealed in under it, though the surface showed no evidence of infection. It seems certain that tonsillar infection is very frequently secondary to dental infection and that the latter should be cleared up before resorting to tonsillectomy. An attack of tonsillitis is frequent after dental treatment. Oral infection may cause redness and swelling to persist about the fauces and pharynx after tonsillectomy.

The importance of septic conditions in the mouth and throat in furnishing the conditions for mixed infections in diphtheria, scarlet fever, etc., is very important.

Persistent bronchitis will improve or disappear at times after extraction of septic teeth. In a case of gangrene of the lungs and putrid bronchitis, Leyden and Jaffé found elements in the sputum which morphologically, as well as in their reaction to iodine, were identical with those which occur in the mouth. Some authorities report pleurisy and empyema due to oral sepsis, and Horder mentions influenza, pneumonia, bronchopneumonia, septic bronchitis and asthma.

Case II.—R. E.: age, 26 years; railway man. At 5 years of age, patient had meningitis. Asthma began 1909, and he has had it ever since, save during 1915, when he was laid up all year with rheumatism in joints, throat, eyes, tongue; partial ankylosis of jaws and nodosities of middle fingers of each hand. Blood pressure, 128-78. Hemolytic streptococcus in tonsils.

September, 1918.—Patient reports very marked improvement following removal of tonsils and septic teeth.

During his illness the following diseases were presented: *oral sepsis*, *tonsillitis*, *asthma*, *rheumatism*, *urticaria*.

The author, with S. Howell, of Welland, saw a prolonged, atypical right-sided pleurisy, accompanied by fever, chills and sweats. There was suppuration about an upper left molar from which a stream of pus could be expressed. Recovery promptly followed extraction.

Pneumonia may be due to extension of a bronchitis, to aspiration of septic material or to hematogenous infection. The fact that pneumococci and streptococci, mutually transmutable organisms, are common inhabitants of the mouth, suggests the latter as a port of entry of infection, not only in lobar pneumonia due to pneumococci, but in cases with mixed infection. The frequent occurrence of *Streptococcus viridans*, associated with pneumococci, *Bacillus influenza* or other organisms, in severe types of epidemic pneumonia, as reported by Cole, Macallum and others, is significant.

Case III.—In April, 1918, a vigorous railway man, age 46 years, was seen by the writer and Dr. Bell, of North Bay practically moribund

Vol. I.—26.

with acute pneumonia. The patient had never before been seriously ill, though the condition of his mouth was horribly septic. Some three days previously, he had had a small epithelioma removed from the floor of the mouth, the surgeon at the same time extracting 3 or 4 loose septic teeth in the upper jaw. He died on the third day, and cultures from the tooth sockets and the operation wound showed *Streptococcus viridans* and a diphtheroid bacillus, and from the right lung a pure culture of *Streptococcus viridans*. Blood cultures were negative.

CASE IV.—More recently a vigorous woman, aged 35, died from a massive, double bronchopneumonia of the cyanotic type, 6 days after extraction of a septic tooth. At the time of extraction a small abrasion of the lower lip occurred, which was followed by diffuse swelling, extending into the submaxillary region. She also developed extensive gingivitis, osteitis and osteomyelitis of the lower jaw.

Tuberculous infection of the submaxillary and mediastinal lymph-nodes of oral origin, with the possibility of secondary pulmonary involvement, should be borne in mind. Oral sepsis may be an important source of mixed infection in pulmonary tuberculosis. Many clinicians have noted asthma associated with oral sepsis, and its improvement after dental treatment. It is usually attributed to anaphylaxis from increased absorption of bacterial or disintegrating tissue products in a patient previously sensitized by the infection.

DIGESTIVE SYSTEM.—A coated tongue, foul breath, salivation, bad taste, various forms of stomatitis, pharyngitis, gingivitis, ulcers on the mucous membrane of the tongue, gums, lips, cheeks, soft palate and fauces may result from oral sepsis. Nausea, flatulency, epigastric discomfort, hyperacidity and other symptoms of nervous indigestion are common.

Gastric disease may be partly due to deficient mastication from loss of teeth, but the swallowing of pathogenic bacteria and hematogenous infection are of much greater importance. Hunter describes a common form of "septic gastritis" due to swallowing of pus, the bacteria in which, owing to perversion in the gastric secretion, are not destroyed, as in healthy conditions. Rosenow's investigations and experiments relating to gastric ulcer would attach more importance to hematogenous infection with septic embolism—a view which now finds more general acceptance. Gastric and duodenal ulcer, appendicitis, colitis, pancreatitis and cholecystitis may all be due to oral sepsis.

There can be little doubt that proper care of the mouth will lessen the frequency of these diseases, make them more amenable to medical treatment and thus lessen the frequency of surgical operations. Cases with a history such as the following are common:

CASE V.—A vigorous man, age 45 years, had suffered from recurring attacks of hyperacidity, hunger-pain and other symptoms suggestive of duodenal ulcer, the diagnosis of which was confirmed by x-ray examination. Operation was advised, but before having it done, he had his septic teeth removed. He began to improve immediately, and eighteen

months later was accepted for life insurance, being perfectly well in the meantime and free from all digestive symptoms.

There can be little doubt that re-infection from the mouth or tonsils is a cause for the recurrence of attacks or recrudescence of symptoms of gastric and duodenal ulcer, gall-bladder infections and appendicitis. It also furnishes a satisfactory explanation of the frequent clinical association of these diseases.

Cases of marked enlargement of the liver itself, associated with recurring attacks of jaundice, fever, etc., occur. A recent case is as follows:

CASE VI.—R. S.: age, 62 years; lawyer. On August 11, 1917, patient had fever up to 103° F. (39.4° C.); frequency of micturition, loss of weight from 165 to 125 pounds; chills; hepatic dullness from 4th rib to level of umbilicus; bile-staining of tissues. Never had any tenderness over the gall-bladder area. Three years ago prostate was removed and several vesical calculi with it. Now shows extreme oral sepsis. Patient failed to respond to prolonged rest in bed with medical treatment and physical condition precluded gall-bladder drainage.

Teeth removed by Dr. Harold Clark, September 25, 1917; followed by extreme collapse, cyanosis and torpidity for a couple of days; a recurrence of chills and fever; blood culture proved sterile. Condition subsided somewhat, to recur later with slight jaundice and bile in the urine with each attack. By February, 1918, patient was much improved; liver had receded to costal margin; heart sounds improved; blood-pressure 100-80; and jaundice gone. Recently a troublesome attack of lumbago and sciatica has confined him to the house. Tonsillitis (*Streptococcus viridans*) in the stumps left after a tonsillectomy, probably accounts for the recurrence of symptoms. The tonsils have been completely removed, with amelioration of symptoms.

During his illness the following diseases were presented: oral sepsis, tonsillitis (*Streptococcus viridans*), cholangitis, cystitis, myocardial weakness, hypotension, 95-75, lumbago, sciatica and albuminuria.

Spastic constipation, intestinal flatulency and discomfort, recurrent attacks of diarrhea, and mucous colitis may occur secondary to oral sepsis.

W. D. Miller says, "In all troubles of the digestive tract, too much care cannot be bestowed on the antiseptics of the mouth."

In the author's series of cases of oral sepsis there were 151 presenting digestive disturbance, in which were included 16 cases of gastric and duodenal ulcer, 5 of gall-bladder and liver infection, and 19 of appendicitis.

CARDIOVASCULAR SYSTEM.—The relationship of tonsillar infection to rheumatism and its cardiac complications has been recognized for years. If tonsillitis is frequently a result of oral sepsis, streptococci being commonly found in both, we must recognize the possibility of diseased teeth directly, or indirectly through the tonsils, being a cause of cardiovascular diseases—endocarditis, pericarditis and myocarditis. Many

clinicians have reported such cases. The *Streptococcus viridans*, as shown by Rosenow, Libman, Horder and others has a special predilection for the heart, where it frequently causes a chronic bacterial endocarditis. Klotz has described a form of aortitis due to the same organism.

In cases of chronic myocardial insufficiency, with or without hypertension, improvement of the cardiac and general symptoms frequently follows on clearing up an oral sepsis, as in the cases reported by Babcock.

CASE VII.—J. G.: male, age, 37 years; steamship agent. Referred by Dr. Solway, November, 1917. Insomnia, severe cough for 5 months, weakness and diarrhea. Mitral systolic murmur. Apex in 6th space in mammary line. No cyanosis. Temperature, 101.4° F. (38.6° C.). Teeth in poor condition; gums very septic looking; tonsils swollen; pharynx reddened; shoulder joints show marked grating. Later confined to bed with temperature up to 102° F. (38.9° C.), and *Streptococcus viridans* was recovered in pure culture from the blood and also from pus around the teeth. A few weeks later the patient died.

During the course of his illness patient experienced the following: oral sepsis, tonsillitis, infective arthritis, mitral disease, bronchitis.

Hypotension occurs at times, possibly, according to Billings, as an anaphylactic phenomenon.

It is probable that oral infection may be a cause of obscure phlebitis and thrombosis in different parts of the body—the eye, brain or extremities.

Chronic lymphangitis, as in cases of pseudo-elephantiasis of the lower extremities, may possibly have a similar origin. A woman aged 40 years, who had never lived outside Ontario, had extensive oral sepsis, with arthritis and other systemic evidence of that disease; and this was the only cause found to account for extreme elephantiasis of the left thigh and leg.

GLANDS OF INTERNAL SECRETION.—The relationship of oral infections to thyroid enlargement and Graves' disease has been independently noted by many clinicians, including Charles Mayo, Crile, Billings, Rosenow, Reed and others. Ehrhard has traced a lymphatic connection between the sublingual and submaxillary glands and the thyroid.

Other sources of infection, and especially the tonsils, are referred to by many authors as affecting the thyroid. Halstead many years ago noted thyroid hypertrophy due to adjacent infection. Beebe, in 3,500 cases of exophthalmic goiter between 15 and 24, found nasopharyngeal infection in 38 per cent. Rosenow found streptococci in 25 out of 32 cases of goiter. In the author's series were 20 cases of exophthalmic goiter, 41 simple goiter and 15 thyroidectomies.

One patient, a young factory woman, with simple goiter, developed marked symptoms of hyperthyroidism a few days after filling of an upper left molar. This had become abscessed and her symptoms promptly subsided after extraction, with copious escape of pus.

Another patient, a nurse about 25 years, developed arthritis in the

knees and feet, for the relief of which infected tonsils were removed, but without improvement. She showed classical symptoms of a moderately severe Graves' disease which, along with the arthritis, immediately began to improve after treatment of several infected teeth.

The tendency for disease in one of the chain of ductless glands to set up trouble in others is generally recognized and usually attributed to the action of hormones. Our knowledge of focal infections, involving tissues similar in structure, suggests that this may explain some cases of polyglandular involvement.

The common association of oral sepsis with diabetes has generally been explained to be due to lessened systemic resistance to pyogenic infections resulting from the constitutional condition, but if oral infection can produce pancreatitis, its influence as a possible cause of diabetes is worthy of consideration. That infection reduces the capacity to metabolize carbohydrates is frequently demonstrated by the recurrence of glycosuria during an acute infection where no change in diet has been made. Osborne, in reporting cases, concludes that glycosuria can be, and perhaps true diabetes may be, caused by mouth infections; and similar views are expressed by Daniel of London, J. S. Marshall and others. Joslin says, "It is common to have diabetes grow worse in the presence of inflammatory conditions about the teeth and gums."

The nervous manifestations of oral sepsis, also arterial hypotension and hypertension, may be aggravated by the coincident derangement in the functions of the thyroid, suprarenals and autonomic nervous system.

ORGANS OF SPECIAL SENSE.—Many eye diseases formerly attributed to syphilis and rheumatism, are now recognized to be due wholly or in part to focal infection.

Colin Campbell says that as long ago as 1902, William Lang taught the danger of infected teeth producing hematogenous infection after cataract operations and attributed choroiditis and uveitis to focal infection. The percentage of eye infections due to dental foci alone is difficult to determine, as syphilis, tuberculosis and diseases in the tonsils, sinuses, middle ear and elsewhere are so common.

Irons and Brown, in 100 cases, estimated that the teeth alone were responsible in 7 per cent. and a contributory factor in 11 per cent. Byers in 25 cases of uveitis (iritis, cyclitis and choroiditis) attributed 5 cases, or 20 per cent., to diseased teeth alone and in 2 other cases they were contributory.

In 70 cases of eye infection in private practice, Campbell considered the teeth alone responsible in 16 cases and contributory in 8, about 33 per cent. in all.

J. M. Levy in 57 cases of eye infection found the trouble on the same side as the dental lesions in every case but one; therefore, he thinks infection is through the lymphatic circulation. Half of his cases improved or recovered after dental treatment.

Zentmayer, de Schweinitz, Goulden, Sedgwick, Blunn, Finnof and many others report cases of uveitis, choroiditis, conjunctivitis, episcleritis, optic neuritis and corneal ulcers due to dental infection.

CASE VII.—In May, 1915, the writer saw a patient, a teacher, age 30 years, who complained of headache and eye pains, following an attack of influenza the previous March. Dr. Campbell found slight but definite optic neuritis. This was the beginning of an illness of nearly three years, during which she had prolonged periods of fever up to 100° F. (37.8° C.), became pale, emaciated and very ill. Her mouth looked healthy and as her dentist, who was attending her twice weekly, gave assurance of the absence of infection, x-ray examination was not made. During her prolonged illness she developed successively *parotiditis* and *right facial paralysis*, *polyneuritis* of the legs, marked *myocardial weakness*, low grade *uveitis*, slight *papillitis*, *exudate into the vitreous*, and *secondary glaucoma*, impairing vision in the left eye and reducing it in the right eye to 6/60. Wassermann and Widal tests and blood cultures were all negative; tonsils fairly healthy. X-ray films in September, 1916, were not conclusive. Patient was not improving. Satisfactory films in February, 1917, showed seven abscessed teeth, which were extracted or otherwise treated, after which her general condition recovered, and the eye infection subsided, but with blindness on the right side and sight in the left permanently impaired.

Otalgia, otitis media, from extension of infection from the throat, tinnitus, vertigo and catarrhal and nerve-deafness have all been reported.

BONES, JOINTS, MUSCLES AND FASCIA.—Osteitis, pericostitis and osteomyelitis of the maxillary bones are among the local manifestations of oral sepsis.

In addition to these, arthritis, fibrositis, spondylitis, myositis, often accompanied by neuritis (so-called rheumatic affections) constitute the commonest group of diseases due to oral infection, being manifested in 25 per cent. of the writer's cases. In 498 cases of chronic arthritis, Moorehead reports that 89 per cent. showed roentgenographic evidence of chronic alveolar abscess and 76 per cent. well-marked pyorrhea.

Any joint, but commonly several, may be involved: the hip, the knees, ankles, shoulders, joints of the hands and feet, spine and others exposed to strain or excess of work are most commonly affected. Goadby, Hartzell and others have described the peculiarities of this type of arthritis. The former says it is a "periarticular arthritis deformans" in which the joint capsules, synovial membrane, ligaments and fibrous-tissue connections are especially involved, though the cartilages are also affected. The disease is characterized by exacerbation and recessions. Fever is often absent; temperature to 102° F. (38.9° C.) or higher, however, is by no means infrequent. Marked effusion into the knee joints may occur, though cultures from the fluid are usually sterile. The destructive changes are such that only in early cases may marked improvement or cure be expected, even though the original cause has been removed. The *Streptococcus viridans* is the common infecting organism. Rosenow and Hartzell have produced the joint lesions by animal inoculation.

CASE VIII.—T. W. E.: male, age 38 years, accountant. Consulted the writer June, 1918, for pain, stiffness and swelling of knees, which

began November, 1917. Patient laid up three months. Had three teeth extracted and was much improved. In May, 1918, condition returned and grew rapidly worse. Ran septic temperature (99° – 101° F. [37.2° – 38.3° C.]) for weeks. Wassermann negative. Culture of blood, negative. Several more doubtful teeth were eventually extracted. Cultures from removed teeth showed *Staphylococcus aureus* and streptococcus, while a *Streptococcus viridans* was obtained from the tonsils. Culture from fluid in joints was sterile. Since removal of infected teeth and clearing up of oral sepsis, patient has improved rapidly and has now returned to work.

The following conditions were present during the course of his illness: oral sepsis, tonsillitis (*Streptococcus viridans*), infective arthritis, sciatica (1900), synovitis (1907).

Tenosynovitis and bursitis are common. A case of severe oral sepsis recently under observation had persistent arthritis in the knees, elbows and joints of the hands and feet, accompanied by marked hammer-toes. Most of the patient's septic teeth had been removed some two years before, but he failed to improve. On consultation with his dentist, the extraction of three other suspicious teeth was decided upon. These were found to be septic. A chronic abscess about an ingrowing tonsil was treated. The patient began to make slow but steady improvement, though from the chronicity of the case, considerable stiffness remains. To one's surprise, with the subsidence of his joint symptoms, the hammer-toes slowly resumed their natural position, the condition evidently having been due to a synovitis of the extensor tendons of the toes.

Goadby says, "The extent of disease and quantity of pus in the mouth bears no relation to the severity of the arthritis. In fact, the free discharge of pus from the alveolar process often indicates a more complete autogenistic reaction than the slow passive insidious rarefaction without copious discharge."

SKIN.—Anemia of varying degrees is common, though the studies of Potter, McNeill and Bradbury suggest that, as a rule, it is not a marked feature.

In well-marked oral sepsis the skin is frequently pale or sallow, harsh and dry. Pigmentation—chloasma or occasionally leukoderma—occur and often show improvement after dental treatment. The hair may be dry and the scalp scaly; cases of alopecia areata have been reported by several authors.

Purpura occurs at times. Some years ago a Hebrew, age 30 years, entered St. Michael's Hospital, Toronto, with mild febrile symptoms following extraction of a septic tooth a few days previously. His condition became worse, accompanied by bleeding from the gums, widespread subcutaneous hemorrhages, hematemesis, melena, hematuria and rapidly developing anemia, from which he died in about a week.

The group of cutaneous lesions and systemic manifestations designated "erythema multiforme" are not infrequent. Some apparently are similar to the so-called "septic" rashes. It is interesting to note

the association which clinicians have long recognized between erythema multiforme and rheumatism (Osler).

Futcher comments on the association of scleroderma, Raynaud's disease and arthritis. McCrae in his analysis of 500 cases of arthritis, found that there were 11 cases in which scleroderma coexisted with the arthritis, and in 5 of them there was also Raynaud's disease. He comments on the rather striking fact that in no instance did Raynaud's disease occur alone, but always with scleroderma.

Urticaria and angioneurotic edema may occur, coincident or alternating with lesions of the erythema group. In the writer's series of cases were 3 in which angioneurotic edema, urticaria and erythema developed pronounced temporary exacerbation of symptoms after extraction or other dental treatment. Five of the cases showed marked symptoms of Raynaud's disease, associated with other systemic manifestations of oral sepsis.

CASE IX.—Miss J.: age, 35 years, teacher. Patient consulted the writer December 15, 1917. Complaint, blanching of toes and fingers, extending up to elbows in winter or while bathing in summer. Skin generally pale, smooth, firm and inelastic, almost "hide-bound" in places; at other times brilliant red in color intermixed with blue. At times patient has large elevated blotches about knees and hips. Had rheumatism of elbows, knees and feet last winter; in bed two weeks. Hemoglobin 80 per cent. X-ray of teeth showed considerable sepsis; four teeth were removed, from which cultures of *Staphylococcus aureus* were grown and vaccine used. The day after removal of the teeth her knees were much worse. Cultures from tonsil crypts and expressed caseous plugs showed *Staphylococcus albus* and non-hemolytic streptococcus. Another vaccine was prepared later and used after tonsils were removed, September 23, 1918. At one time patient had marked edema of legs, especially at boot tops, which later quite cleared up. There was some improvement, but she still showed evidence of dental infection.

March 15, 1919.—Three remaining doubtful teeth have been removed and cultures made from them showed *Streptococcus viridans* and *Staphylococcus aureus*.

The following conditions were evidenced during the progress of the case: oral sepsis, tonsillitis (*Staphylococcus aureus* and *streptococci*), Raynaud's disease, infective arthritis, anemia 80 per cent., erythema multiforme, thyroid enlargement.

CASE X.—Mrs. F.: age, 40 years. Patient consulted the writer August 21, 1918, with paresis of left upper and lower extremities, numbness of left leg up to knee, general weakness and headache. Wassermann reaction of blood and spinal fluid both negative. Hemoglobin 85 per cent.; albumin, casts and pus in urine. Some swelling of face. Thin nervous person, with tremor of fingers. No atrophy of left side, and no sensory changes. Tenderness over left musculospiral nerve. Some grating in both knees; several very septic teeth were removed in November, 1918, and a *Streptococcus* and *Staphylococcus albus* grown. Thy

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 mild slightly enlarged; eyes slightly prominent; pulse 120; marked tremors.

March, 1919.—General condition greatly improved since removal of septic teeth.

Edema of the extremities and symptoms of scleroderma or pseudo-elephantiasis occur at times. A marked example of the latter, involving one lower extremity, slowly developed after a dermatitis in the leg. The patient, a female, 35 years of age, had never been in the tropics, and had never suffered from any serious disease. Heart, lungs, kidneys and pelvic organs showed no evidence of disease. Wassermann test negative. She had had much trouble with her teeth since her fifteenth year, many of them being devitalized, dark in color and filled. Several root abscesses were present and cultures from these and the tonsils showed *Streptococcus viridans*.

Another woman, school teacher, age 30 years, had marked oral sepsis. *Streptococcus viridans* and *Staphylococcus aureus* being obtained from the teeth and *Streptococcus viridans* from tonsils. She also has infective arthritis of the knees, recurring erythematous eruptions and pronounced symptoms of Raynaud's disease involving the fingers, hands, forearms, feet, ears, nose and lips. The skin in other parts of the body was unusually firm, inelastic, somewhat thickened, pale, smooth and glossy. The thyroid was slightly enlarged.

Many cases of persistent eczema show marked improvement or cure under treatment which has been unsuccessful before the oral sepsis was cleared up. In a series of 50 cases of skin disease, Chapman found evidence of focal infection in 49, 35 of whom had abscessed teeth alone.

Daland and others mention furunculosis due to oral sepsis; and rosacea, various form of lichen, psoriasis, acne, dermatitis herpetiformis are all reported by various authors as being at times related to or aggravated by mouth infections.

Pruritis, apart from any definite cutaneous lesions, is a common manifestation of oral sepsis.

Whatever the relation may be, there is no doubt of the clinical fact that many erythematous and inflammatory skin diseases show marked improvement after focal infections in the mouth or elsewhere have been removed.

KIDNEYS AND URINARY TRACT.—The relationship of tonsillar infection to nephritis is well recognized, and more recently diseased teeth have been equally incriminated. These focal infections are frequently accompanied by albuminuria, casts and blood in the urine, and may cause an acute nephritis or set up chronic renal disease with associated cardiovascular phenomena. Hartzell and Henriei and Rosenow have produced suppurative and hemorrhagic lesions in the kidneys in animals by inoculation of *Streptococcus viridans* from the mouth. Lecount and Jackson report acute, subacute and chronic renal changes in rabbits after inoculation by streptococci obtained from the throats of patients suffering from angina in an epidemic due to milk infection.

In all cases of infection of the urinary tract, oral sepsis and other focal infections should be carefully sought for. Goadby has reported streptococci in the urine in cases of rheumatoid arthritis.

A railway conductor, age 45 years, who had never suffered from any previous illness, was rejected for life insurance on account of much albumin, numerous red blood-cells and a large amount of pus being found in the urine. On ureteral catheterization both kidneys were found to be involved. The phthalein output in two hours was 30 per cent. Bacteriological examination and animal inoculation of the urine obtained by catheterization were negative. Patient had extreme oral sepsis; hemoglobin 90 per cent.; physical examination otherwise negative. Condition promptly cleared up after extraction of the septic teeth.

Recurrent renal hemorrhage occurs at times.

NERVOUS SYSTEM.—The nervous symptoms associated with oral sepsis include a group presenting the clinical picture of psychasthenia or neurasthenia, including sensations of weakness, lassitude, early fatigue, mental depression, flushing, dizziness, insomnia, cardiac arrhythmia and tachycardia, gastric and intestinal flatulency, uncomfortable epigastric sensations, neuralgias, painful spine, frontal, vertical or occipital headache and kindred ailments. These may be due in part to toxemia acting upon the brain and nerve centers and in part indirectly through disturbed function of the thyroid and other glands of internal secretion. Perusal of Beard's monograph on neurasthenia (1880), in the light of our present knowledge, suggests that many of the symptoms which he described as characteristic of that disease are now recognized as due to oral sepsis or other focal infection. He observed the frequency of dental disease in neurasthenia but considered it a *result* rather than a *cause* of it. He says: "Among all classes of brain-working indoor-living Americans, the teeth usually begin to decay before the age of 20; and it is quite rare to find a nervously exhausted person, however careful he may have been of his teeth, who can exhibit a really sound set at the age of 35 or 40. It is more probable that, if he has any teeth of his own at all, very many of them are filled; perhaps some of them in several places, and their endurance will depend upon the skill with which the filling has been done."

Among the symptoms of neurasthenia, he mentions nervous indigestion with severe pain before meals, relieved by taking food; gastric and intestinal flatulency; growing pains, pains in the back, coccydynia, podalgia; dryness of the joints with creaking sounds on movement; pruritis, dryness, scaliness and scurfiness of the skin. He states further that "neurasthenia may simulate rheumatism, and has been frequently mistaken for it. Thus stiffness of the neck, when the upper portion of the spine is in an irritable condition, or of the loins and lumbar region when the lower part of the cord is irritated, at once suggests rheumatism." No experienced clinician at the present time would consider neurasthenia *per se* a satisfactory explanation of symptoms such as the above. It is further interesting to note, according to Beard's observations, that neurasthenia occurs most frequently at the time of life when

oral sepsis is most marked. "Neurasthenia seems to be most common between the ages of fifteen and sixteen and forty-five and fifty. It is found in those under, but comparatively speaking it is rare and different in its character at extremes of life." While stating that "American dentists are the best in the world because American teeth are the poorest in the world," he did not recognize the possibility that mouth infection might be a cause of the "American disease."

Neuritis, especially of the brachial and sciatic nerves and spinal nerve-roots, is common. Rosenow has shown experimentally that herpes zoster may be produced in animals by injecting them with streptococci from tooth infections. Neuritis is frequently associated with or simulated by arthritis in a neighboring joint, by spondylitis, fibrositis or myositis. In cases of brachial neuritis, grating may usually be obtained by manipulation of the shoulder joint and at times synovitis may extend along the sheath of the long tendon of the biceps, causing pain on movement of the arm. The optic, 3rd, 5th, 6th facial, auditory and perhaps other cranial nerves may be involved.

The numbness and tingling in the hands and feet in pernicious anemia are believed by Hunter to be due to the accompanying oral sepsis, and the explanation may apply at times to peripheral neuritis occurring in diabetes, gout, and other constitutional diseases.

Instructive cases are reported by Duke, of the effect of oral infections in contributing to the symptoms of tabes and of improvement following upon dental treatment.

Focal hemorrhages, myelitis and softening, degenerative or sclerotic changes in the spinal cord, and cases presenting the symptoms of disseminate sclerosis are reported by Rosenow, Billings and others.

Rosenow has produced in dogs focal hemorrhages, ataxic gait and paresis of the extremities, by the injection of streptococci obtained from the tonsils in a case of disseminate sclerosis.

Meningitis, encephalitis and abscess of the brain are mentioned by Miller and others. The relationship of oral sepsis to cerebral thrombosis and softening is worthy of investigation. Pearce Gould has recorded a case of death from alveolar abscess resulting in thrombosis of the cavernous sinus.

Migraine, epilepsy, tic douloureux and chorea are diseases in which many observers mention oral sepsis as a factor, though in the two former reflex disturbance from the pressure of unerupted teeth is perhaps more important (Figs. 56 and 57).

H. S. Upson, H. A. Cotton and others have reported remarkable results in the management of mental deficiency and psychoneurotic manifestations in the young, in nervous instability, alcoholism and cases of insanity, by treatment appropriate for the extreme sepsis, deformities, unerupted teeth and other forms of dental trouble so frequently found among this class of the population.

Diagnosis.—Diagnosis may be considered under two heads: (a) local; (b) systemic.

(a) **LOCAL DIAGNOSIS.**—The local or regional diagnosis is established by the systematic examination of the teeth, gums, alveolar sockets, mucous membrane of the mouth, the tongue, tonsils, pharynx, sinuses, the submaxillary lymph-nodes, as already outlined. There are 32 teeth in the adult presenting 30 possible avenues of infection, each of which should be investigated. Special attention should be directed to dentures, crowns, bridges, filled or pivot teeth, and devitalized or dead teeth, as the latter are especially prone to infection. The abutments of bridges require close attention.

It must not be forgotten that a mouth in which much dental work has been done may present an outward appearance of being well kept and healthy and yet be the seat of extensive periapical infection. The importance of roentgenological examination and care in the interpretation of films has been considered elsewhere. The size of the area, the



FIG. 56.—UNERUPTED SUPERNUMERARY TOOTH PRESSING ON ADJACENT POSTERIOR MOLAR.



FIG. 57.—IMPACTED TOOTH SHOWING INFECTION AND ADONTOMATA ASSOCIATED WITH EPILEPSY.

number of teeth involved, or the amount of pus present bears no necessary relationship to the seriousness of the condition. All old roots and snags are septic. It is especially necessary to keep these facts in view in dealing with cases where the symptoms fail to clear up after the major part of the sepsis has been removed, but where a few doubtful teeth remain. Moreover, the infection may persist in the tonsils, lymph-nodes, maxillary bone, sinuses or other secondary foci.

The possibility of periapical abscess secondary to systemic infection, and of infected pulps in the absence of caries should not be overlooked.

Bacteriological examination of infected pulps, the discharge from abscesses, pyorrheal pockets, tonsils, and the roots of extracted teeth should be made whenever possible. The coöperation of a dental expert is often imperative and always advisable.

(b) **SYSTEMIC DIAGNOSIS.**—The systemic diagnosis is made on general clinical lines, applicable to the different organs and tissues involved. The result of appropriate dental treatment is very important, though the failure to improve does not warrant the conclusion that the original infection was not of oral origin.

Constitutional diseases, such as scurvy, diabetes, indigestion, gout,

anemia, poisoning by lead, mercury and other conditions predisposing to disease of the gums and teeth should be kept in mind.

Prognosis.—The prognosis has been dealt with in discussing the pathology of oral sepsis, systemic manifestations, x-ray examinations and extraction of teeth, and, therefore, does not call for detailed discussion.

(a) **LOCAL CONDITION.**—The opinion of a competent dentist is of the greatest value in determining the limitations of conservative treatment, or whether extraction is necessary; and when the services of such are available he should take the responsibility of advising the patient. Where the systemic condition does not clear up after dental treatment, the dentist should be prepared to reconsider the case with the physician, from the systemic as well as from the local viewpoint.

(b) **SYSTEMIC CONDITION.**—As Billings has pointed out, infected lymph-nodes or other organs or tissues may serve as secondary foci which continue the systemic infection. One should never promise results, but take his stand on the ground that an infection in the mouth, as elsewhere in the body, should be cleared up, whether by conservative or radical means, depending upon one's ability to deal with it.

The degree of improvement to be anticipated in the heart, kidneys, joints or other organs or tissues which are involved depends upon the length and severity of the infection, the amount and nature of the damage which has been done, and on the existence of permanent secondary foci of infection. In many cases functional cure will of necessity be incomplete. The patient's age and general health have an all important bearing upon prognosis. Many individuals with extensive local infection may be practically free from symptoms of general disease.

Treatment.—**ORAL PROPHYLAXIS.**—The recent awakening of the medical and dental professions, and the public at large, to the menace of mouth infections and the difficulties, often amounting to impossibility of successful conservative treatment in cases of pyorrhea and caries, where the gums, pulp, dental canals and periapical tissues are seriously diseased, has impressed upon all the necessity for thorough prophylactic measures, especially in the young. Dental inspection of school children and dental clinics are carrying out important educational propaganda and providing treatment for poor children. Specially endowed institutions for research, treatment and propaganda are springing up in various centers and have an important field of usefulness in relation to public health. The removal of enlarged and infected tonsils, adenoids and other causes of mouth breathing is important. All are agreed as to the necessity for carefully brushing the teeth several times daily, so as to avoid accumulation of putrefying food and bacteria. The tooth brush requires more attention. It is usually too large to be effective. The bristles may be stiff, causing injury to the gums; and too little attention is given to its proper disinfection, which should be done in alcohol or boric-acid solution between use.

A. E. Webster has pointed out a general wearing away of the enamel with advancing years, from the use of gritty tooth pastes and brushes with too hard bristles. The incautious use of acid and other

medicines corrosive to the enamel should be borne in mind. Careful hygiene of the mouth during acute illnesses as well as in chronic debilitating diseases is important. Overindulgence in sugar and carbohydrate foods, which furnish pabulum for lactic-acid fermentation is worthy of attention; also drugs having a specific action on the gums, as mercury and lead, should be used with discretion. The difficulty of dealing successfully with caries, periapical infections and pyorrhœa alveolaris impresses one with the paramount importance of careful prophylaxis in the young in dealing with the problem of mouth infections.

EXTRACTION OF TEETH.—The removal of teeth is a serious matter, interfering with mastication and, consequently, limiting the kind of food the patient can eat, thus interfering with his digestion and nutrition. From the cosmetic point of view also it is important. Some patients find it difficult or impossible to use dentures for mastication or in speaking.

The shock, the opening up of fresh areas for the absorption of pathogenic bacteria and their toxins, involved in the removal of one or many infected teeth—especially in the old, the debilitated and in cases of acute systemic infection—are matters for serious consideration. The amount of trauma and subsequent infection is often greater in extracting sound teeth.

General infection, pneumonia, suppuration of cervical glands, osteomyelitis, periostitis and necrosis of the maxillary bones, extensive gingivitis, the stirring up of acute symptoms in the joints, the appendix, gall-bladder, heart or other tissues, are possibilities to be borne in mind. The removal of unerupted teeth, especially, is often a difficult and serious procedure.

These points are brought forward, not as arguments against necessary extraction, but that it should be undertaken only for definite reasons, in the case of each tooth, and with due care and appreciation of serious possibilities.

In cases of severe extensive local infection, it is safer to clean up the field of operation as far as possible by preliminary treatment. As a rule it is better not to extract in the presence of acute local disease, or acute systemic infections, as the increased absorption of infective organisms which follows often leads to aggravation of symptoms. Where the patient's general condition is not good, many teeth should not be extracted at one time. Serious illness or death from sepsis following extraction is by no means rare. While these results may be due to the condition necessitating the extraction and therefore, as in other surgical operations, the risk is warranted, yet the tendency on the part of the public is to attach blame to the operation, rather than to the infection requiring it. In general, the opinion of a competent and experienced dentist should decide as to the limitations of conservative treatment and the necessity for extraction.

At present there is a tendency toward reckless and indiscriminate extraction on insufficient grounds and for all sorts of ills which should be guarded against. J. M. Anders warns the medical profession of the

reaction likely to follow reckless and ill-considered sacrifice of the teeth.

Definite indications for extraction have not yet been agreed upon by dentists. Can an abscessed, devitalized tooth be treated conservatively so as to be free from present or future danger? Were the question asked with reference to a septic foreign substance in another part of the body, where the conditions as to circulation and local nutrition are more favorable, the answer unquestionably would be in the negative. Rhein describes an elaborate technic by which devitalized teeth may at times be retained without danger of infection, but such treatment is not within the reach of the large mass of the people.

When periapical infection occurs, if not too extensive and if properly treated, most dental authorities agree that conservative methods are available. The greater the degree of pericemental involvement at the apex, and especially if accompanied by a chronic suppurative pericementitis (pyorrhea) extending alongside the tooth, the greater the danger of failure from conservative treatment and the more likely will extraction be necessary.

Recent investigations do not bear out Miller's opinion that the bacteria in a closed root-canal either perish, or, what happens more rarely, become inactive as soon as the nutriment in the pulp is consumed, i.e., in a few days.

According to Rhein, if the pulp contents are absolutely removed, any pathogenic tissue present eradicated, and the canals hermetically sealed in such a manner that the sealing material is forced through the apical orifices thus obliterating them, no infection will ensue, but "whenever the roentgenograph does not show the periapical end of the root-canal to be absolutely sealed, the operation must be considered a failure . . . and the tooth should be immediately extracted, or the unfilled portion of the root be removed by an apicoectomy."

The necessity for the greatest degree of surgical cleanliness, the avoidance of unnecessary trauma, the provision for proper drainage and protection of the wound and the use of antiseptic mouth washes following extraction are important points to be kept in mind. The failure to remove necrotic tissue or pieces of roots will prolong infection and is often a cause for future trouble.

The Surgeon and Oral Infections.—The importance of oral sepsis in surgical and obstetrical practice has not received the attention from specialists in these departments which its importance warrants. It can scarcely be doubted that it is a frequent source of postoperative and *postpartum* infections, and yet how infrequently are the mouth and other sites of focal infection considered in these cases. Talbot, in a study of 97 cases, states that the immediate cause of the symptoms of the toxemia of pregnancy is "the retention of the normal physiological waste products of the developing pregnancy. The primary cause, or the cause of the retention, is the inhibitory effect of the toxins of chronic sepsis on the excretory functions of the kidneys." Waller has called attention to the influence of oral sepsis in producing deficient lactation

and as a cause of obscure persistent vomiting in infants. The presence of *Streptococcus viridans* in cases of fibrocystic ovaries has been reported and oral and other focal infections may have a bearing on the causation of cystic mastitis.

Infected tonsils are commonly removed without reference to the presence of dental infection, which is often the primary seat of trouble; operations are undertaken in the most septic mouths without previous oral preparation. The same statement applies to thyroidectomies for Graves' disease and operations for gastric and duodenal ulcer, gallstones, appendicitis, etc. The trauma associated with operations produces lessened local resistance to infection, so that focal infection probably accounts for certain cases of pus formation in wounds.

Except in cases of emergency it should be the duty of the operator to assure himself that points of focal infection have been cleared up as far as practicable before any important operative procedure.

Hartzell says it is wrong to undertake grave surgical operations for persons whose mouths and gums are pouring a flood of microorganisms into both stomach and circulation. This is especially necessary in operations about the mouth or neck.

If oral sepsis stands in etiological relationship to a common group of surgical diseases, oral prophylaxis and treatment undoubtedly will tend to lessen their frequency and insure better postoperative results.

The occurrence of epithelioma of the tongue, lips, gums or other tissues exposed to the irritation of carious roots, and projecting teeth with coincident infection, has frequently been noted.

Insurance and Oral Sepsis.—As yet insurance companies have not seriously considered oral infection in their selection of risks; but having in view the investigations of recent years showing the frequency with which serious diseases may be due to this cause, the question is bound to receive more attention in future. This applies especially to cases with a previous history of rheumatism, heart trouble, appendicitis, gastric and duodenal ulcer, biliary infections and goiter.

Life insurance examiners should carefully observe and report on the condition of the teeth and other evidence of mouth infections or systemic manifestations associated therewith.

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CHAPTER X

PRACTICAL URINALYTIC METHODS AND THEIR SIGNIFICANCE

BY MARTIN H. FISCHER, M.D.

Introduction, p. 423—The importance of urinalysis, p. 424—The collection of the urine, p. 424—The preservation of the urine, p. 425—Physical characteristics of the urine, p. 426—Acidity determinations, p. 433—Acetone bodies, p. 440—Reducing substances in the urine: Sugar, p. 445—Proteins in the urine: Albuminuria, p. 453—Microscopical examination of the urine, p. 465—Summary, p. 469.

INTRODUCTION

It is not the purpose of these pages to add to the already long list of chemical manuals available on the examination of the urine by physical, chemical and other scientific means. They express, rather, an attempt to state what the general man in medicine or surgery *can* do in the way of urinalysis and *will* do for the patients committed to his care. What is suggested here is, in a certain sense, the irreducible minimum which must be done for every patient if an approximation, even, of correctness in diagnosis, guide to treatment, and a fair knowledge of what is happening to the patient is desired. *The interests of the general man in medicine or surgery have been alone considered.* The points touched upon are, therefore, in no sense exhaustive, and the methods described are often not the best that could be employed. *But they are the simplest that can be used and so little time-consuming that no conscientious worker in medicine will neglect them.*

There will be launched against what is here written the criticism that many more or better procedures could have been followed. This is cheap knowledge not to be gainsaid, for to know and to do much for a patient is obviously better than doing less. This is, however, not the matter at dispute. The following pages are intended to bring home that it is better to do what is here outlined than that which is done more commonly—namely, nothing at all.

It is a fair statement that several approximately correct analyses made by the attending physician himself will be more informing to the physician and will be a better guide to treatment in certain diseases than a single more careful analysis made at a distant laboratory by a man who has not access to the patient. An analysis of the urine to the distant laboratory worker is, of necessity, too much of an end in itself; and the author knows, through experience, that the cryptic tables mailed to the attending physician are, in most instances, mis-

understood or misinterpreted and so of no value whatsoever to either him or the patient committed to his care. The only way out is for the analyst and the physician to consult over the patient or else for the physician to become enough of an analyst to discover for himself the elementary things so necessary for his guidance. The latter ideal is in no sense an impossible one and it is in this spirit, of accomplishing more for the patient, of giving more help to the busy practitioner and this in such manner as not to make inordinate demands upon the patient's purse or the physician's time, that the following pages are written.

THE IMPORTANCE OF URINALYSIS

Proper examination of the urine derives its great practical importance from the fact that through it we obtain not only an index of various changes which may be occurring in the kidney or in the genito-urinary organs which connect this viscus with the outer world, but because in the urine we also find the evidences of changed body chemistry as incident to poisoning of various sorts and to the different diseases like the "metabolic" disorders which accompany improper utilization of proteins, of carbohydrates or of fats in the body.

But from the fact that so many and such widely varying changes in all or a part of the human mechanism may thus mirror themselves in the physical or chemical properties of the urine, there arises a difficulty—that of judging properly the real significance of any given urinary finding. But even in this, knowledge of and proper utilization of a few guiding principles clear a main road which any one may follow and one which the traveler may subsequently decorate with as many exotic shrubs as may please his special fancy. The experienced traveler and the safe guide is not the man who knows every path, but he who is sure of the main one. The serious errors of our profession are not those which are incident to the non-discovery of rare and unusual types of disease; as every one knows who follows his patients beyond the bedside and through the autopsy room, our errors are more gross, and cover long-known and well-marked pathological disturbances. Pregnant women with milk-sugar in the urine are treated as diabetics when anything but a restricted diet should be their share; diabetics are tortured with the false interpretations placed upon the fractional "per cents." of reducing substance which they show in the urine; and the well-to-do in expensive hospitals die of as real starvation as the famished of India, because the meaning of acetone bodies in the urine is not clear to the attending physician.

THE COLLECTION OF THE URINE

Since the twenty-four-hour period is the unit cycle of our physiological existence, it is for most purposes the best unit of time to choose

for an examination of the quantitative and qualitative output of urine. Shorter periods, because they do not cover the daily habit of the human machine as regards work and rest, feeding, etc., are likely to be fallacious. There are, however, some important exceptions to this rule. Whenever certain changes are more intense at one period in the day than at another a special examination at such time will give light where the examination of the twenty-four-hour sample may have failed. Traces of sugar in a mild diabetic are most easily found an hour or two after partaking of a meal containing carbohydrate; traces of albumin in the ordinary "nephritic" are commonest in specimens obtained before breakfast, because through the night the urine attains its highest acidity; on the other hand, in the "orthostatic" albuminurias such traces are best found in specimens voided when the patient is up and about, and when, in consequence of such endeavor, the acid content of the urine has been raised above the average, or even night level.

To obtain a twenty-four-hour sample some hour of the day should be settled upon, like eight or ten in the morning, at which time the patient should void naturally or be catheterized and *this urine be discarded*. All subsequent voidings are then collected in clean (preferably steamed and distilled water-washed) vessels, the last voiding being timed to coincide with the hour at which the twenty-four-hour period was started.

THE PRESERVATION OF THE URINE

Urine should not be preserved, but be examined as fresh as possible. A few minutes suffice to bring about changes in urine which may be significant and a few hours may so disturb the value of a whole series of tests as to make them meaningless. Urine from an infected genito-urinary tract may, through ammoniacal decomposition, for example, give false readings as to acidity, urea content, presence of casts, and nature of original sediment; while a normal urine may, through infection with bacteria, begin to show a positive albumin reaction as this is synthesized in the bodies of the microorganisms from the simple nitrogenous compounds present in all urine.

If, in spite of such facts, urine must be preserved, cold storage is least harmful and the use of sterilized containers will do much to prevent undue bacterial contamination. Five or ten drops of formaldehyd added to a pint of the secretion often works well. But under such circumstances a positive "sugar" test (Fehling's test) becomes meaningless, for formaldehyd reduces such alkaline copper solutions. A few crystals of boric acid added to two or three ounces of urine retard bacterial development, but boric acid changes the acidity of the urine and therefore the value of all tests regarding this. A few drops of chloroform, a little camphor or a few crystals of thymol will preserve small volumes of urine, but even these substances interfere with certain tests (like those for traces of albumin) or they prove inadequate in really preventing bacterial or other decomposition.

PHYSICAL CHARACTERISTICS OF THE URINE

Quantity.—The urine must always be regarded as composed of (a) water, and of (b) dissolved substances. Urine, in other words, is not a unit but the complex of these two elements. In large measure the secretion of the water and the secretion of the dissolved substances are independent of each other. Instead of saying a kidney secretes "a large amount of urine of low specific gravity," or "a small amount of urine of high specific gravity," it is better to say a large amount of water containing a small amount of dissolved substances or a small amount of water containing much dissolved matter.

The secretion of water by the kidney is in essence its first function, for without such water secretion, no dissolved substances of any kind can be put out by this organ. *A good water output by the kidney is, therefore, the best first evidence of its functional capacity.* The secretion of dissolved substances is secondary to this. This holds not only for the normal substances appearing in the urine, as sodium chlorid and urea, but even for all such "foreign" substances as potassium iodid, milk-sugar, methylene blue or phenolsulphonephthalein when used for functional testing. In other words, a kidney incapable of excreting water properly will never be able to put out any of these dissolved substances properly.

On the other hand, a kidney may be functionally entirely adequate and yet various dissolved substances may not be excreted properly. This is because many and widely differing factors, lying entirely outside of the kidney, may render impossible a proper excretion of any normal product of metabolism or any foreign substance (like a dye) injected to test "kidney" function. Thus it is often said that a kidney is functionally below par because the excreted urine, while sufficient in amount, is not sufficiently rich, absolutely or relatively, in urea. It is too often forgotten regarding the patients upon whom such remarks are made that the amount of urea in the twenty-four-hour sample of urine is even normally dependent entirely upon the amount of protein consumed. If the amount of protein intake is reduced, the urea excretion must be reduced in like measure. All urea determinations are valueless and all conclusions based upon such determinations are fallacious unless the protein intake of the individual is known. Because of lack of appetite, of inattention to feeding or because the patient is in coma, there is commonly, in the ill, a physiologically entirely inadequate intake of proteins. If instead of taking the normal daily average of 125 grams of protein, a hospital patient takes or receives only one-half or a quarter of this amount, the total urea output will also be but one-half or one-quarter the normal. But obviously, if such a low urea output is discovered, it is not to be laid to a kidney insufficiency as is so commonly done, but solely to the physiological consequences of such a reduced diet.

These things considered, it becomes clear why a proper determination of the quantity of water given off by a kidney in each twenty-four-

hour period is one of the best, if not the best, evidence of its functional capacity. To make sure that judgment regarding a given output is not fallacious, the following physiological facts must be borne in mind:

Under physiological conditions water is taken into the body, in the case of the human being, only through the mouth. Not only is water drunk as such, but large quantities are carried in with our food, or are subsequently formed in the tissues through the oxidation of hydrogen-containing foods (like the carbohydrates and fats) to water. Water may, however, get into a patient by other means. Thus it may be given by way of the rectum in enemas or drips, either as plain water or as so-called "physiological" salt solution. It may also be absorbed from the serous cavities. The older surgeons, for example, frequently left a quart or two of "physiological" salt solution in the peritoneal cavities of laparotomized patients.

The water from any or all such places is absorbed into the blood and carried to the different tissues of the body. *Only a part, and this not the major part, is lost through the kidney.* This fact is constantly forgotten by physicians and all manner of erroneous conclusions follow.

Water may be lost from the body (a) through the lungs, (b) through the skin, (c) through the kidneys, and (d) through the bowel. Element d may be ignored if there is not a diarrhea or when cathartics have not been administered to increase the normal loss of water through the bowel. For the rest, the amount of water lost through the kidneys is dependent upon the absolute amount of free water available for excretion minus the amounts lost through the lungs and skin. But let it not be thought that these are insignificant as compared with those lost through the kidneys. From the lungs is ordinarily lost as much or more (namely, 2,000 c.c.) (68 ounces) than from the kidneys, and the skin pours out from a third to one-half as much as the kidneys (namely, 500 to 750 c.c.) (17 to 25 ounces). The remainder, from all the water taken in or formed in the body (namely, 1,500 to 1,800 c.c.) (51 to 61 ounces) goes out through the kidneys.

Other things remaining constant, less urine will obviously be lost through the kidneys if the activity of the lungs or the skin is increased, and *vice versa*. For this reason, a hot day decreases the urinary output of even normal individuals and a cold day increases it. Or, to make the illustration fit the bedside case, a *fall* in amount of urinary output is to be expected regularly after the successful "sweating" of a patient.*

Since the urinary output is thus seen to be the balance between total water intake minus total water loss from other organs, the following important diagnostic conclusions may always be drawn from a study of the quantity of water put out by the kidneys:

1. The secretion of 1,500 c.c. (51 ounces) or more of water by the kidneys in each twenty-four-hour period justifies the conclusion that

* Why an increase in water output is obtained later when such sweating is applied to an "acute nephritic" is dependent upon the better oxidation chemistry (better blood supply) which follows in the kidney after this has been dehydrated through the sweating. For a detailed discussion of this question see Martin H. Fischer: "Edema and Nephritis," 2nd Edition, John Wiley and Sons, New York, 1915, p. 555.

they are possessed of an adequate functional capacity. This remains true so far as the kidneys are concerned, even if the amounts excreted run to 2,000 or 3,000 c.c. (68 or 102 ounces) or more, and whether the specific gravity of the urine be low or high. It is true even if the urine contains much albumin or many casts. The reasons for this will become clearer as we proceed, but it may be stated even now that less than one-quarter of the total kidney substance (more nearly one-eighth), properly preserved, will maintain all normal urinary secretion, both as to water and to dissolved substances. Animals or human beings so operated upon that one-half of one and all of the opposite kidney have been removed live indefinitely and are perfectly normal so far as all functional tests are concerned, as long as the remaining fragment of kidney is normal. Conversely, a normal water output from the kidney means that at least such a physiological minimum is doing its work well.

2. The secretion of amounts of urine lying below 1,500 c.c. (51 ounces) in the twenty-four-hour period needs investigation, but amounts as low as 500 c.c. (17 ounces) need not yet mean functional incapacity of a kidney. They may mean simply that the patient is not getting much water (as drink, food or by rectal injection), or that he is losing much through lungs, skin or bowel. To see if the kidneys are really at fault in a doubtful case, a quart of water should be given. If the urinary output jumps up some 200 to 500 c.c. (7 to 17 ounces) during the next two hours, the kidneys are *not* at fault. If the secretion remains low, the kidneys may yet not be affected; the body of the patient may simply not be saturated with water, so that none is left over out of which to make a urinary secretion. The quart of water may, therefore, be given a second time at the end of the two hours' wait. If the water output does not jump up this time, the kidney efficiency (for either direct causes, as in generalized parenchymatous nephritis, or indirect causes, as in a decompensated heart with a bad circulation through the kidney) may definitely be considered below par—a conclusion readily confirmable by further study of the urine and the patient himself.

Color.—Urine is of a pale yellow color because of a pigment which it contains. Since the amount of this pigment, which is formed every twenty-four hours, is fairly constant, the intensity of the straw color of the urine goes down or up with every increase or decrease in water excretion. In cold weather, after the patient has partaken of much water, and when the total water output is high in consequence of such diseases as diabetes mellitus, diabetes insipidus or arteriosclerosis ("chronic interstitial nephritis"), the urine is paler than normal; in hot weather, on the other hand, and in all pathological states which decrease the water output (as heart disease, anemia, parenchymatous nephritis, etc.), the urine is deeper yellow in color than the normal.

The yellow color becomes still deeper or even brownish when, in consequence of the infectious diseases, *urobilin* appears in the urine. A more than normally bright yellow urine follows the administration of rhubarb or senna. Red urine indicates the presence of blood (oxyhemoglobin), though care must be taken not to be led astray by the red

color given urine by various synthetic drugs. Knowledge of what the patient is taking and microscopic examination of the urine for red blood-corpuscles will help in the differentiation. If the hemoglobin of the blood has suffered chemical change to methemoglobin or hematorporphyrin, the red color gives way to a more brownish one. Fresh hemorrhages, as in lesions of the lower urinary tract, therefore, usually give pinkish or distinctly red urines; while older hemorrhages, due to diseases higher up (as in the kidney or in the blood itself), are more apt to give less red and more brownish urines. Poisonings with various coal-tar derivatives commonly used in medicine, or with carbolic acid or resorcin, frequently yield "smoky" urine.

Methylene blue, when used for kidney testing or as a urinary antiseptic, gives the urine a greenish color; phenolsulphonephthalein gives a bright yellow or red color, depending upon the acidity or alkalinity of the secretion.

Odor.—The odor of normal urine is familiar to most individuals. The change following the consumption of asparagus and due to the excretion of methylmercaptan is of no significance. It is amusing to note that no other ground than the development of this unpleasant odor seems ever to have been found for eliminating this vegetable from the dietary of victims of "kidney disease." Acetone can sometimes be smelled in the urine. Since its presence is of great importance from a diagnostic, prognostic and therapeutic point of view (*see below*), it is well to make a mental note of such a finding. The smell of ammonia in the freshly voided urine indicates decomposition of the urea, and is due usually to infection of the urinary passages or of the urine itself after being voided. When less obviously present it may mean a high degree of generalized acid intoxication ("acidosis").

Turbidity.—Freshly voided urine when normal is usually clear. This is true even of the mixed twenty-four-hour specimen. Individual samples, as after meals when much acid is being poured into the stomach, may be turbid. This is because the urine at this time tends to become more alkaline and so various phosphates are precipitated. The matter is tested by adding a little acetic acid to the turbid urine. If due to phosphates, the turbidity clears.

Even normal urine may become cloudy if chilled. This is especially true of the more concentrated urines as seen in patients who are drinking little or perspiring much. It is also true of the concentrated urines of patients who are the victims of severe heart disease or generalized kidney disease with decrease in urinary output. In such urines, the white, pink or red precipitates of the various urates settle out because of their lessened solubility in cold water. If the turbidness is due to urates, it will disappear on warming the urine.

Turbidity may also be due to bacteria, to large numbers of formed elements like white or red blood-corpuscles, or to globules of fat. Microscopic examination (which *see*) will quickly give aid here.

Specific Gravity.—Specific gravity determinations are usually to be made upon the mixed twenty-four-hour specimen of urine. For this

purpose a small hydrometer of the proper range and known as a *urinometer* is used. The urine to be tested is ordinarily poured into a special cylinder, but if a larger glass or conical graduate is available, it is really better. No foam must appear on the surface of the urine. If such is present, it should be skimmed off with a bit of clean filter paper. The urinometer, which should be absolutely clean, is now immersed in the urine and given a spin, care being taken to see that the neck and scale of the instrument are moistened to a sufficient height by the urine. Before the specific gravity figure is read off, it is made sure that the instrument is floating free, not having attached itself to the side of the cylinder. The reading is made from the *lower* line of the meniscus.

Under normal conditions the specific gravity of the twenty-four-hour mixed sample of urine is supposed to lie close to 1.015. It may vary, however, between 1.010 and 1.025, not only from day to day, but from hour to hour in the same day. In alleged pathological conditions, the extremes may run from 1.002 to 1.060.

Specific gravity determinations upon the urine, while readily made, probably more often lead the practitioner of medicine to false conclusions than to correct ones. This is because it is too largely forgotten of what the specific gravity is a measure and what factors in the case of the urine influence any or all of the values found.

The specific gravity of the urine is a rough index to the amount of material dissolved in the water of the urine. Distilled water being taken as unity (1.000), every substance dissolved in such water (except such as have by themselves a *lower* specific gravity than water) *raises* the specific gravity of the liquid. The amount of increase in specific gravity over that of pure water varies, not only with the kind of material dissolved in the water, but with its concentration.*

If the type of the dissolved materials is fixed (like urea and various salts, for example), specific gravity measurements become an index of the amount of such dissolved substances in the unit volume of the solvent (water).

With these things and a few physiological facts clearly in mind, it will now be apparent of how much (or how little) significance the ordinary specific gravity determinations are.

It is in the urine that certain ultimate products of body chemistry (like urea) are thrown off, plus those elements of the diet which are not used in the elaboration of heat or other types of energy in the body (namely, the "ash" or salts taken in with our food), and it is to the presence of this urea and the various salts that urine owes the fact that its specific gravity exceeds that of distilled water or 1.000. Conversely, the specific gravity may be used to calculate the total solids in the unit volume of water. For this purpose the figures of the second and third decimal points are multiplied by 2.33 (Haeser's coefficient), the answer given being the amount of solids in grams per liter. Thus

* It varies also with the temperature, but this element is commonly ignored in clinical analyses.

urine with a specific gravity of 1.015 would contain 15×2.33 , or 34.95 grams of solids in the liter. If the patient voided 1,500 c.c. of urine in the twenty-four hours, his total solid output for this period would be 52.42 grams.

The calculation of the total solids thus put out is probably the best one value which specific gravity determinations can yield us, but even it does not ordinarily mean much. The reasons for this are as follows:

The amount of solids lost in the urine is dependent primarily upon the total food intake, for it is this which determines not only how much protein is taken, from which urea may be produced in the body, but the total food intake determines also how much of various salts will be freed in the body to be lost through the urine, the bowel or the skin.

Other things being equal, a low total solids output merely means that the patient is not eating the average amount, either because he is ill and so does not swallow or properly use his food, or because enough food is not being furnished him. If, for example, the ordinary adult who, on 125 grams of protein plus his ordinary carbohydrate and fat ration, excretes 1,500 c.c. urine of a specific gravity of 1.020, suddenly takes only half this amount of food (with water intake and loss kept constant), there follows a fall in specific gravity which, if the volume of urine voided remains the same, will give the urine a specific gravity close to 1.010.

Where the mistake is made in these specific gravity determinations is in assuming that such apparent deviations from an assumed "normal" specific gravity mean, if too low, "kidney" disease (like chronic interstitial nephritis); if too high, diabetes mellitus or some other disease. While such conclusions may be correct, they should be drawn more slowly.

Obviously, everything which makes for a decreased intake of food, and, therefore, for a decrease in the total solids available for giving a specific gravity of more than 1.000 to the water being given off by the kidney, is going to make for a urinary secretion which has a low specific gravity. Urine of low specific gravity need never surprise us, therefore, in patients badly fed or underfed (this includes most hospital patients on a "light" diet), in patients unable to eat (as gastric carcinomas, acute and chronic infections, persistent nausea, comatose individuals, etc.), or persons who are voluntarily or involuntarily undergoing starvation (mental cases, patients being starved for gastric ulcer, etc.).

On the other hand, even if the food intake is normal in amount, a more than usual excretion of water by the kidneys will again yield a urine of low specific gravity. Habit in water drinking may by itself be sufficient to yield a "large daily output of urine with low specific gravity." Not only heavy water drinkers, but heavy drinkers of coffee, tea or beer come in this class. It would be absurd in such persons and on such evidence alone to think the kidneys affected.

Cold weather (with decrease in water loss by way of the skin and lung) increases the water output by the kidney: wherefore the specific

gravity of the urine in cold weather is uniformly lower than in warmer weather. If a better circulation through the kidneys and a poorer one through the skin or lungs is brought about by a psychic state (as in fear or hysteria), the net physiological result is again the same—more water voided as urine and this of a lowered specific gravity.

In diabetes insipidus we have also (for, as yet, unknown reasons) such a large water output by the kidney; wherefore the urine of these individuals on the average diet is also of low specific gravity.

Such facts will suffice to show why, even when the secretion of much urine of low specific gravity is persistent, it need not yet mean "chronic interstitial nephritis." When the latter diagnosis seems justified because high blood-pressure, cardiac hypertrophy and occasional casts with a little albumin confirm our suspicions, it must still be clearly kept in mind that such high secretion of water is an index of *good* kidney function and that if the total solid output corresponds with the intake, everything is to be looked upon as favorable *so far as the kidneys are concerned*. If a bad prognosis is to be made, it must be made upon other findings than those shown by the urine.*

Reverse conditions will, on the other hand, yield urines low in quantity and (in consequence) high in specific gravity. As a matter of fact, if the diet is average, all low water outputs by the kidneys are uniformly associated with a high specific gravity of the secretion. Sweating will bring about this result whether due to hot weather, a hot pack or a high fever. A psychic state with vascular dilatation of the skin blood-vessels will do it. If the vascular dilatation follows a bigger than usual dose of alcohol, the kidney secretion will again mirror the fact.

All pathological conditions which make for a restricted water secretion by the kidney also work toward this end. It is for this reason that the output of little urine with a high specific gravity is common to all conditions which make for an increased capacity of the body tissues to hold water, as incident to the "acidoses" consequent upon all the anesthetics, the intoxications with alcohol, or the intoxications with the products of various acute infectious diseases. Because such "acidoses" appear also in the severe anemias, the cardiac decompensations and the poisonings with the various heavy metals,** the urinary findings are again the same. And this is true also of the secretion coming from those kidneys which are the victims of an acute or chronic "generalized parenchymatous nephritis"—essentially an edema of the kidney parenchyma produced by the same poison or poisons which elsewhere in the body may have given rise to an edema there.

Only one type of specific gravity finding in the urine would seem to justify a single and that an undebatable type of conclusion. This

* The alleged consequences of kidney disease are touched upon below. For a more detailed discussion see Martin H. Fischer: "Edema and Nephritis," 2nd Edition. John Wiley and Sons, New York, 1915, p. 482.

** For references to the literature, see in Bibliography Martin H. Fischer: "Edema," p. 122; "Nephritis," pp. 52, 173, 186; "Edema and Nephritis," pp. 425; H. B. Weiss; William deB. MacNider.

concerns the output of large amounts of urine of a high specific gravity. In the pathology of the human organism we know of but one such picture and that appears when more than the usual amount of solid substance appears in the urine following even the normal or average intake of food. In diabetes mellitus the carbohydrates cannot be utilized in normal fashion in the body, but persist as dextrose and are in this form thrown off in the urine. Even though such an individual drinks a greater than usual amount of water (because of the dehydrating effects of the sugar upon the tissues, and the thirst produced thereby), the amount of solids in the urine may still remain so high in the unit volume of water as to yield a urine of persistently high specific gravity. But the trouble here is not in recognizing the possibilities of having before us a diabetic under such circumstances; the real danger lies in being lulled to sleep from the opposite type of findings and thus being made to miss a diabetic who, even with sugar, shows no material increase in the specific gravity of his urine. It is for this reason that, even in diabetes, one qualitative Fehling's or other sugar test is worth a thousand specific gravity readings.

Summed up, we may therefore say that, if the diet is not properly considered, all specific gravity measurements are worthless; that if the diet is considered, the specific gravity is of importance only as this is multiplied by the amount of urine put out. A kidney putting out a liter of urine at 1.020 is functionally just as good as one putting out two liters at 1.010 and *vice versa*. If the kidney is going to be blamed, it must be done only after all the physiological and pathological factors which lie outside of the kidney and which determine separately the amount of water that comes to the kidney for excretion and the amount of dissolved substance that comes to this organ for the same purpose have been properly judged and disposed of. The golden rule remains: *When in doubt, judge the kidney functionally normal if it is yielding a proper amount of fluid, no matter what its specific gravity.*

ACIDITY DETERMINATIONS

Titration Acidity.—An abnormal production or accumulation of acid in some or all of the organs of the body, and acting upon the colloids found here, is so essentially the underlying cause of edema and of diseases which in essence are nothing more than edemas (for example, uremia, glaucoma, nephritis, etc.), that some simple clinical method of recognizing the existence of such an abnormal production or accumulation of acid and of gauging its intensity is of the greatest importance.

We have not at present any methods which can be used clinically for directly measuring changes in the acid content of the different organs of the body. We can, however, measure the acidity of the blood which bathes them as well as the acidity of the different secretions from the body, as the urine, saliva and sweat. Other things remaining the same, the laws of chemical equilibrium then permit us to conclude, from such

variations, that there must have been similar changes in the tissues from which they came. Thus, an increase in the acidity of the urine means, generally speaking, an increase in the acid content of the kidney from which it came, and *vice versa*.

We have now to say exactly what we mean by urinary "acidity." In the days before physical chemistry, acidity and degree of acidity were usually measured by titrating with an alkali of known strength. This gives the so-called *titration acidity* of a liquid, and this type of analysis has been applied to the urine, as to many other fluids derived from the body. The titration of such a liquid as urine is not, however, an easy matter, for it owes its "acidity" not so much to the presence of a certain amount of "free" acid, as to the presence of a series of so-called "acid" salts (in other words, salts of a polybasic acid, like phosphoric, in which only a part, like one atom, of the replaceable hydrogen has been neutralized by a base). Even the best methods (which too often introduce considerable error because they call for the addition of water, of various salts, or of other materials to the urine which modify the acidity) are not free from criticism. Nevertheless, such titrations will yield important results *if the physician will do them*.

A titration, which for clinical purposes is sufficiently accurate, can easily be made by adding to 25 c.c. of the urinary sample one or two drops of a 0.5 per cent. solution of phenolphthalein in 50 per cent. alcohol and then titrating with one-tenth normal sodium hydroxid until a permanently pink color is obtained.

The capacity of the urine for thus neutralizing alkali varies greatly through the twenty-four hours. Generally speaking, it is lowest just after meals and highest just before meals, after exercise and through the night. When mixed twenty-four-hour specimens are compared, normal urines do not ordinarily take up more than 20 to 30 c.c. of one-tenth normal sodium hydroxid per 100 c.c. of urine.

Because urinary titrations take time, and because, if they are to be of any service to the patient, they must in many instances be done frequently (perhaps several times daily in the acute cases), such analyses are likely to be ignored. Carelessness in this direction is further fostered by the statement that such determinations are of no value, anyway. The practitioner is in this way tempted to let the whole matter of a quantitative determination of acidity slide by him or to content himself with dipping a strip of litmus paper into one or more samples. But since all human urines, with the exception of those voided just after meals, show an acid reaction to this indicator, not much is thus learned regarding any abnormally high acidities which, either because of their intensity or because of the length of time which they persist, are likely to prove dangerous to certain organs in the patient's body (as in glaucoma, uremia or acute nephritis) or to the life of the patient himself.

The titration acidity of the urine has by scores of investigators been found to run much above that of normal urine in a large number of

diseases (as in heart and respiratory diseases, in anemias and infections, in diabetes and nephritis, etc.) and may to this day be used to advantage in the study and therapy of such clinical states. Objections to its use are found in the previously expressed shortcoming that a really careful employment of titration methods is too time-consuming for the average practitioner and, second, in the fact that *the titration acidity of the urine is not an absolute guide to the degree of acid intoxication occurring in the body as a whole or in the kidney in particular.*

The reasons for this are, of course, obvious. When, for example, we compare the poisonous effects upon living tissues of equivalent concentrations of phosphoric acid, ammonium dihydrogen phosphate, diammonium hydrogen phosphate, and triammonium phosphate, the first is found to be highly poisonous, the second more mildly so, and the third and fourth still less poisonous, in the order named. Yet the titration acidity of all four, *as ordinarily determined* by titrating with standard sodium hydroxid solution, gives the same reading. These facts must be kept in mind when judging the clinical significance of the titration acidity of the urine. For, clearly, were a urine filled with pure, highly poisonous phosphoric acid instead of the comparatively innocuous dibasic or tribasic salt, the titration acidity would not betray the fact. Determination of the titration acidity has nevertheless a distinct value if what has been said be kept in mind. It is capable of giving us definite evidence of the existence of an abnormally high acid content in the urine (and therefore in the kidney or the body as a whole) and of the changes in this from hour to hour or day to day. Titration acidity does not, however, as the above facts show, vary *directly* as the degree of intoxication, and only ignorance of the elementary facts of chemistry would ever lead any one to expect such complete parallelism.

Hydrogen-ion Acidity.—The physical chemists have more recently distinguished between the *latent* and the *active* acidities of a fluid, meaning by the first the total replaceable hydrogen, by the second the hydrogen-ions yielded upon solution in water. When the physical chemists speak of acidity they usually refer to the active or hydrogen-ion acidity, and a large portion of them believe that all so-called acid effects are dependent exclusively upon the presence and the number of these hydrogen-ions. When the acid content of a system is increased, there follows usually an increase in the hydrogen-ion acidity. Increasing the amount of acid in a beaker of water is followed by an increase in the number of hydrogen-ions, and when we deal with very dilute solutions the increase in hydrogen-ion acidity is very nearly proportional to the increase in the amount of acid. It is for this reason that the hydrogen-ion acidity of urine coming from a kidney containing a more than usual amount of acid, either because of nephritis, or because of a more generalized acid intoxication in the body, is usually increased. The increased acid content of the kidney, to satisfy the laws of chemical equilibrium, demands an increased acid content in the urine coming from it, and as an expression of this we find an increased hydrogen-ion acidity. The hydrogen-ion acidity of the urine can be meas-

ured in various ways, and, since some of these can be used clinically, it constitutes *one* figure of value in judging a kidney case.

It must, however, be clearly understood from the outset that hydrogen-ion acidity determinations of the urine can alone be no absolute index to the severity of the acid intoxication occurring in the kidney or the body as a whole, nor yet that every increase or decrease in hydrogen-ion acidity is or must be followed by a corresponding increase or decrease in the severity of the acid intoxication. The reasons for this are, of course, obvious. The attempt was made some twenty years ago to show that the toxicity of various acids, as determined by their effects upon growing plants, the sense of taste, the absorption of water by muscle, the aggregation of infusoria, etc., followed their degree of ionic dissociation. It was early learned, however, that no such parallelism exists. Thus it was found that acetic and other organic acids with their low dissociation produced physiologically as great effects as the highly dissociated hydrochloric, nitric, and other acids. On the other hand, the rather highly dissociated sulphuric acid produced physiological effects far below the weakly dissociated organic acids. In other words, *physiological effect is not determined solely or even in the main by the degree of dissociation.* The author was the first to show that an entirely similar disproportion between degree of ionic dissociation and effect produced, holds for the swelling of various protein colloids, and in so doing emphasized that the observed physiological reactions depend, in the main, upon the protein constituents of the tissues under consideration.

It would, therefore, have been manifestly absurd for the writer to have claimed that any physiological effect could be measured by merely determining quantitatively the hydrogen-ion acidity, and this whether we deal with purely physiological reactions or with the question of the development of the signs of a nephritis in a kidney. An increase in the hydrogen-ion acidity of the urine above a normal standard may serve as evidence of an abnormal acid content in the kidney itself, but it can never be a complete measure of the degree of the intoxication. To make the matter more concrete, we need but illustrate this by saying that on poisoning an animal or a kidney with hydrochloric acid there occurs a great increase in the hydrogen-ion acidity of the urine, yet if we produce a similarly great intoxication by the use of lactic acid only a slight rise is observed; on the other hand, intoxication with sulphuric acid again gives us a great rise in hydrogen-ion acidity, and yet comparatively little effect on the animal or the kidney.

To these considerations needs to be added the further fact, so often emphasized by the writer, that an increase in the acid content of any organ in the body, as the eye, brain or kidney, does not alone determine the degree of effect produced. *The presence and kind of salts found in that organ influence markedly its swelling, its "solution" and the degree of incapacitation of its function and mere measurement of the hydrogen-ions in the urine tells us nothing of these factors.* As a matter of fact, the addition of salt (even of neutral salt) to an acid-protein mixture brings about an actual rise in hydrogen-ion acidity of

the liquid about the protein as this shrinks. The same fact can at times be observed clinically when a temporary rise in the hydrogen-ion acidity of the urine follows the active administration of salt alone. Unless such simple principles of physical and colloid chemistry are borne in mind, we shall never come to a correct understanding of the value and limitations of such hydrogen-ion determinations.

Of the methods that have been or may be used to measure the hydrogen-ion acidity of the urine (or any other body fluid), nearly all are too complicated for routine clinical use.

To get a method which would yield for clinical purposes sufficiently accurate data and still be simple enough to be employed by any one, the writer used graded indicators such as the physical chemists employ.* By using a number of dyes which show color changes at definite hydrogen-ion concentrations and then using the same indicators on the urine, it is possible to determine its hydrogen-ion acidity. The indicators are so chosen that their turning points vary from each other approximately by the power of ten. Of the many indicators which might be used, those are best which do not give colloid precipitates when added to urine. The following series, the end points of which are sharp and can be readily recognized even in highly-colored urine, have given excellent results in the writer's hands.

INDICATOR SERIES FOR DETERMINING HYDROGEN-ION CONCENTRATIONS IN URINE OR OTHER BODY FLUIDS

Name of Indicator and Method of Preparing Same	Concentration of Hydrogen-Ions When Indicator Changes Color	Color of Indicator	
		In Acid Solution	In Alkaline Solution
Methyl orange (0.5 gram in 100 c.c. distilled water)	10^{-4}	Salmon pink	Orange-yellow
Paranitrophenol (2 grams in 100 c.c. alcohol)	10^{-5}	Colorless	Greenish-yellow
Sive's red ¹ (2 grams in 100 c.c. water)	10^{-5} to 10^{-6}	Red	Canary yellow
Methyl red (0.2 gram in 100 c.c. alcohol)	10^{-5}	Magenta red	Canary yellow
Rosolic acid (0.5 gram in 50 c.c. alcohol, 50 c.c. water)	10^{-7}	Orange-yellow	Magenta
Phenolphthalein (1 gram in 100 c.c. alcohol)	10^{-8}	Colorless	Bluish-red
Thymolphthalein (0.5 gram in 100 c.c. alcohol)	10^{-11}	Colorless	Blue

¹ This is the hydrochlorid of paramonomethylaminonazobenzeneorthocarbonic acid. It does not turn until a hydrogen-ion acidity more than that necessary to turn methyl red is attained, and yet shows an acid reaction before such is discoverable with paranitrophenol. Under the direction of Lauder W. Jones, B. Sive worked this out to meet the need for an indicator lying between these points.

In practice, 10 c.c. of urine are placed in a clean vessel (preferably a porcelain dish, which, if distilled water is not available, is first rinsed in the urine to be tested) and two drops of one of the indicators are

* See Arthur A. Noyes: *Jour. Am. Chem. Soc.*, 1910, xxxii, 815, where is given an excellent discussion of the whole question of measurement of hydrogen-ion acidity. See also Eduard Salm; Fritz Glaser; S. P. L. Sörenson; L. J. Henderson (*Bibliography*). For a further discussion of the clinical side of the question than is here possible, see Martin H. Fischer: "Edema and Nephritis," p. 635.

then added to it. By trying successive indicators one is finally found toward which the urine is neutral. The urine has then the hydrogen-ion concentration represented by the turning point of that indicator. As the acidity of the urine runs up, it will, of course, show an acid reaction to the upper members of the list, and as it runs down, to the lower. The turning point of the commonly used litmus is about that of rosolic acid. Urine, not acid to phenolphthalein, is alkaline to litmus, while thymolphthalein still remains colorless in urines which are distinctly alkaline to litmus.

As is to be expected, the hydrogen-ion acidity of the urine shows great variations even in health. A man doing muscular work, or on a predominantly meat diet shows a higher acidity than one in bed or on a predominantly vegetable diet. The urine after meals is less acid than that before meals, and the night and early morning urines are more highly acid than those obtained after breakfast. The measurement of the hydrogen-ion acidity of the urine is one of the few tests in which averages and twenty-four-hour samples give us *least* information, and one *less* valuable than isolated tests at frequent intervals. The reasons for this are obvious. An athlete starting with a urine alkaline to methyl red secretes one highly acid to this shortly after going to work. But the urine returns to the originally alkaline state after a short rest. In the period of observation the urine originally free of albumin and casts becomes rich in these and then loses them again. Had we measured only the *average* acidity as obtained by mixing the three samples of urine, we should never have discovered the acid wave and perhaps maintained that the hydrogen-ion acidity never went above the normal, as do some of the author's critics. The same is true of the alleged "physiological" and orthostatic albuminurias. At bed-rest the urine shows a degree of hydrogen-ion acidity which increases as the patient assumes the erect position (while albumin, casts, etc., appear at the same time), to fall again on resumption of the horizontal. Only many tests at frequent intervals will betray these constant changes.

What we are interested in particularly, therefore, are the highest acidities registered and *the length of time these remain active*. Other things being equal, it is these two factors which determine how much effect is going to be produced on the colloids of the kidney.

In practice, when shall we say our patient does not exceed a safe hydrogen-ion acidity of the urine? To get at this value the author chooses the highest hydrogen-ion acidity registered by healthy men on a full diet at bed-rest. Such individuals do not show a hydrogen-ion acidity sufficient to turn methyl red to the acid side except, perhaps, in the night urines voided between two and seven in the morning. The urine of healthy individuals who are up and about and on a full diet is also alkaline to methyl red for most of each twenty-four hours, though for obvious reasons, muscular exercise, high meat and fat diets, etc., may increase these hydrogen-ion acidities.

In actual practice, therefore, methyl red should be used as the routine indicator for all urines. Those which, for the major portion of each

twenty-four hours, or always, have an acidity above this point the writer considers abnormally acid. Figures below this point and down to the turning-point of litmus or phenolphthalein he considers normal. Phenolphthalein rarely shows an alkaline reaction (if ammoniacal decomposition of the urine is not present) unless alkali is being fed to the patient. When the urine becomes alkaline to thymolphthalein, too large quantities of alkali are being given, and the possibility of getting an albuminuria due to alkali is at hand.

When methyl red is used in routine fashion on all patients, it will be observed that a large number run constantly acid to this indicator. This serves to bring home how common are low-grade types of acid intoxication. The acute and the protracted infections, starvation cases, diabetics, patients with cardiac and respiratory disease, and patients with generalized parenchymatous nephritis, all show an abnormally high hydrogen-ion acidity. In ambulatory patients with chronic interstitial nephritis secondary to vascular disease such an abnormal acidity may be lacking, even though casts and albumin be present in the urine. In the later stages of the disease, especially when the circulation is beginning to fail, a high hydrogen-ion acidity is the rule. When the acidity of the urine lies constantly below the turning-point of methyl red, or when by the administration of alkali it can be made to do so and be kept there, it augurs well for the patient. On the other hand, *the author cannot recall a single patient in whom it was difficult or impossible to hold the urinary acidity below that of the turning-point of methyl red who did not die.*

The correlation between increase in the hydrogen-ion acidity of the urine and the appearance of albumin and casts in it (*see below*) can be easily observed in athletes who voluntarily produce much acid, as well as in patients with orthostatic albuminuria, or in heart cases showing the first evidences of insufficiency. After exercise or on assumption of the erect position the acidity mounts from somewhere below the turning-point of methyl red to a place above, and if this is maintained for a little time casts and albumin are likely to appear. The more definitely neutral the urine before such added efforts, the longer does it take for the casts and albumin to appear.

If the facts here outlined are borne in mind, the simple methods of measuring the hydrogen-ion acidity described prove of much clinical use. They apprise us of the existence of low degrees of acid intoxication in patients in whom we do not ordinarily look for such. By recognizing and meeting them by dietary regulations and alkali, we increase the reserve of these patients against the effects of such further intoxication as may be due to infection, anesthesia, or the trauma of operation. Or, in the established case, a fall in the hydrogen-ion acidity of the urine tells us that our therapy, so far as alkalizing the patient is concerned, is of a successful type. Since the indicator method is exceedingly simple, we can follow the patient's condition from hour to hour, an important fact when we deal with the acuter manifestations of nephritis and allied conditions. In cases of complete suppression,

in other words, when there is no urine to tell us when we have succeeded in getting an adequate amount of alkali into our patient, *the reaction of the saliva serves as a useful guide*. Ordinarily this is neutral to litmus paper, but it turns acid in various intoxications. Alkali should be given until it again turns neutral or even slightly alkaline to this indicator.*

ACETONE BODIES

(Acetone, Beta-Oxybutyric and Diacetic Acids)

Introduction.—The acids which appear in the urine are in part the normal or physiological products of the chemistry of the body, in part of abnormal nature.

Under the first heading come, for instance, phosphoric and sulphuric acids, which are formed for the most part through the oxidation of the phosphorus and the sulphur found in the various proteins. With other things unchanged, a high protein diet will, therefore, tend to make the total acidity of the urine (whether measured by titration or by hydrogen-ion determination) run up, because such a diet increases the amount of sulphuric and phosphoric acids formed in the body. Mere increase in consumption of protein need not, however, at once mirror itself by an increased titration or hydrogen-ion acidity, as discussed in the previous section, for it all depends upon the amount of alkali available in the body, or consumed with the protein, as to how much overplus of acid will be present. For this reason the ordinary mixed diet, which contains enough alkali in the vegetables and fruits that go with it, yields a total mixed urine but slightly acid or nearly neutral, for the alkali of the vegetable side of the diet neutralizes almost exactly all the overplus of acid resulting from the oxidation of the proteins. Finally, when for the ordinary mixed diet there is substituted the so-called vegetable or milk diet, the overplus of alkali may so far exceed the production of acid that a urine distinctly alkaline in reaction may be voided throughout the twenty-four hours. Man is then like the herbivora which for this reason secrete normally an almost persistently alkaline urine.

Abnormal Acids of the Urine.—Among the abnormal acids found in urine, two groups deserve special attention. The one of these is represented by lactic acid, the other by beta-oxybutyric and diacetic acids. A qualitative test for lactic acid is readily made, but it is of too little importance to the general practitioner to demand this effort. But a qualitative or quantitative estimate of at least some one of the second group is of tremendous importance; wherefore this should be made regularly.

Acids of the type of lactic acid appear in individual organs of the body or in the body as a whole whenever there is an interference with

* The ordinary litmus paper is well-nigh worthless. It should always be tested for its sensitiveness before dependence is placed upon it. Only the neutral litmus paper of the best manufacturers has proved of service in the writer's hands.

the normal oxidation processes in the involved parts. Lactic and other acids may in consequence appear under a large number of widely differing circumstances. They will appear, for example, whenever the intake of oxygen by the whole organism is shut down directly, as in poisoning with inert gases like hydrogen or nitrogen, or when there is a gross interference with the intake of oxygen, as in edema of the glottis, pressure of an aneurysm upon the bronchi, etc. A lack of oxygen to the body may also be induced, even in the presence of an abundance of this gas, if the oxygen absorbing powers of the blood are reduced. We shall therefore have lactic acid in the urine in the severer anemias, after large hemorrhages, or in poisoning with carbon monoxid. Again, the oxygen supply may be plentiful, the oxygen carrying power of the blood normal, but the functional capacity of the heart so low as not to guarantee an adequate circulation. In all uncompensated heart lesions, therefore, be they due to valvular lesions, to muscular lesions or to pericarditic effusions which embarrass the action of the heart, a lack of oxygen will be manifest, from which all the body tissues will suffer, resulting in an abnormal production of lactic and other acids in them, and these acids will appear in such urine as is excreted. What is true for heart lesions is true also, of course, for respiratory lesions which interfere mechanically with the intake of oxygen, like extensive pleuritic effusions or large pneumonias.

Finally, there is possible a local abnormal production and accumulation of lactic and other suboxidation acids in any tissue if its oxygen supply is shut off directly (as in arteriosclerosis or pressure of a tumor upon the afferent or efferent blood-vessels) or more indirectly through intoxication of the parenchyma of the organ which, even in the presence of a normal circulation, results in an inadequate utilization of the oxygen in that organ. It is not ordinarily remembered how many "diseases" are in essence nothing but such local edemas due to a swelling of the involved tissues following an abnormal production and accumulation of acid in them. Under this heading belong parenchymatous nephritis (edema of the kidney), glaucoma (edema of the eyeball), "uremia" (edema of the brain), passively congested liver (cloudy swelling of the liver), etc.

In all these conditions we may get all the effects of a suboxidation acid poisoning in the organs, though for obvious reasons the total production of acid may be too small to mirror itself in the urine voided by such a patient.

The fate of this lactic acid and of the other suboxidation acids thus formed in the body is the same as that of the more normal phosphoric and sulphuric acids. If enough alkali is present in the body these acids are neutralized as formed, and the effects of the intoxication with the lactic acid may in consequence be much reduced or inhibited entirely. It is for this reason that a proper and frequent examination of the urine, to determine whether its total acidity is being maintained at a safe distance below the highest normal level, is of such great importance; the adequacy of an alkali therapy is determined exclusively by

such investigation of the urine. *Alkali must be fed in sufficient amounts to keep the urinary acidity well below that of the turning point of methyl red, no matter how much is required.* The normal human being needs but 5 to 10 grams ($\frac{1}{6}$ to $\frac{1}{3}$ ounces) of sodium bicarbonate in each twenty-four-hour period to accomplish this purpose, but persons with heart disease, diabetes, carbon-monoxid poisoning, mercury poisoning, etc., may require 100, 150 grams ($3\frac{1}{4}$, 5 ounces) or even more to accomplish the same result.

Mechanism of the Production of Acetone Bodies.—The origin of acetone and of beta-oxybutyric and diacetic acids needs to be borne in mind in order to recognize how much may be accomplished by even a qualitative test for any one of these three substances in the urine. The three materials are closely allied from a chemical point of view, usually appear simultaneously and are derived from a common source. A qualitative test for any one of them, if properly made, may, therefore, be taken to indicate that all three are present in the specimen examined. *The importance of finding one of the acetone compounds in the urine lies in the fact that such discovery indicates the existence of carbohydrate-starvation on the part of the organism.*

When we test by titration or with graded indicators the acidity of the urine, we do not, of course, know whether this acidity is due to the normal phosphoric or sulphuric acids, to lactic acid, or to diacetic, or beta-oxybutyric acid. So far as the effects of the acids are concerned, they all tend to kill the organism. From this point of view we are, therefore, not concerned with their quality. We simply give enough **alkali** to neutralize all these acids as formed and let it go at that. But as conscientious practitioners, we cannot stop here. We are interested also in the *mechanism* by which the acids are being produced, for we need to know this in order to better control such acid production. A knowledge of what the factors are which bring about the acid production is, therefore, highly important.

We have already observed how a high acidity due to phosphoric and sulphuric acids may be reduced by cutting down the intake of protein. A reduction in acidity, when due to lactic and this group of suboxidation acids, can be brought about only by giving the patient a better oxygen supply or by aiding him to a better utilization of oxygen in the body. Obviously such a result is brought about only by a removal of the condition or conditions which are making for the interferences with the oxygen supply. It is for these reasons that we order fresh air for the anemic, bed-rest for the cardiac patient, and antidotes in poison cases.

When a patient is being poisoned by beta-oxybutyric and diacetic acids, we can inhibit the process only by improving the conditions which make for better utilization of carbohydrate in his body or by cutting down or out the substances out of which these acids are chiefly formed (fat). Sometimes it is not possible to do as much in this direction as we might wish (as in the severer diabetics), but there is a widespread and definite interference with a proper utilization of carbohydrate

in a large number of individuals who are in no sense diabetics, but are ill in other directions. Sugar-starvation, moreover, is induced in a large number of patients through bad feeding alone, and since a patient is just as dead if starved to death through bad feeding as he is if he dies from diabetes, the recognition of the existence of a carbohydrate starvation is of paramount importance.

It is now generally held that acetone, diacetic and beta-oxybutyric acids are derived from the fats. Under normal circumstances the fats which we eat or have stored in the fat depots of our body are burned to carbonic acid and water; carbonic acid (in the form of carbon dioxide) is lost through the lungs without cost to the body so far as alkali is concerned; water is similarly lost through some excretory channel like the skin, lung, kidney or bowel. In order, however, to have the fat burn to these ultimate products, a simultaneous burning of carbohydrate is required. The older physiologists used to express this fact by saying that "fat burns only in the fire of carbohydrate." When, for any reason whatsoever, the carbohydrate fire is not kept burning in the body, some or all of the fat ceases to be burned to carbonic acid and water; it is only partially burned, resulting in the so-called acetone bodies (acetone, diacetic and beta-oxybutyric acids). *The discovery of acetone compounds in the urine means, therefore, that an inadequate amount of carbohydrate is being burned in the body, or that a disproportionately high amount of fat is being fed the individual.* These facts are of importance not only in diabetes, where they have long been used for diagnostic and for therapeutic purposes, but they are of even greater importance in innumerable other medical and surgical conditions where the difference between the *status quo* and that of the institution of proper carbohydrate feeding is, at the worst, the difference between discomfort and comfort, and, at the best, the difference between death and life itself.

Counteraction of Acetone Production.—In diabetes we have the picture of an organism which, in the midst of plenty of available carbohydrate, is unable to use a sufficient amount of it, in the severer cases, to make possible a proper burning of the fat to carbonic acid and water. In the case of the diabetic, therefore, after we have once allowed him an amount of carbohydrate which will just satisfy all his capabilities for using such, we can cut down or stop the production of acetone compounds only as we *eliminate fat from his diet*. It is for this reason that in recent years the elimination of fat from the diet (as particularly well emphasized by Allen) has become one of the first and most important rules in the treatment of diabetes.

The author, in his practice, makes it a rule, after this first elimination of fat from the diet, to cut down the carbohydrate, but only to the point where the patient will just spill a trace of sugar. (See the succeeding paragraphs on sugar in the urine.) Such a combination of low fat intake, with full utilization of such powers of carbohydrate metabolism as the patient may have left, will obviously yield the lowest possible amounts of the acetone bodies.

But the presence of acetone, beta-oxybutyric, or diacetic acids is discoverable in an enormous number of conditions in which proper administration of carbohydrate will suffice to do away with the condition entirely. Or, to turn the matter about, a large number of patients, through inadequate carbohydrate feeding alone, are made ill, or bad medical or surgical risks, or, to put it flatly, are actually killed by being given an insufficient amount of carbohydrate daily.

It is just as disastrous for the human body to be deprived of an adequate intake of carbohydrate by any of a large number of circumstances, as not to be able to use this carbohydrate properly after being taken in, as is the case in diabetes. The insane, for example, who starve themselves, the individuals with esophageal obstructions who can swallow nothing, the patients who with gastric or duodenal ulcers are not allowed anything, the eclamptics, comatose or nauseated individuals who cannot or will not take proper amounts of food, individuals who, like the surgical patients, are being "prepared" for operation by being kept upon a wholly inadequate "light" diet in our ordinary hospitals—all these show the presence of acetone compounds in their urines. Such acetone compounds also appear when, in consequence of acute or chronic infections, the carbohydrates are not fed in adequate amounts or, if so fed, are not properly used in the body. Undoubtedly, in the past, our typhoids, our chronic pus cases and our patients with the severer types of tuberculosis as often succumbed from carbohydrate starvation as from the diseases themselves.

These points are emphasized because the presence of acetone compounds in the urine calls for an active administration of carbohydrate. In the case of the diabetic, of course, the point to which such carbohydrate administration may be pushed has definite limits set upon it; but in the case of the other conditions enumerated above we need have no such fears. It is too often forgotten how much carbohydrate must be consumed daily by the average individual in order to keep the balance. Generally speaking, 500 grams (a pound) are needed. This figure should be kept in mind because it brings home how perfectly inadequate are our ordinary schemes when active mouth feeding cannot be used daily. The body, moreover, runs short of carbohydrate very rapidly. Two or three days are already bad. The patient who is being starved, either because insane, because the victim of some gastrointestinal lesion, or because he is persistently nauseated or vomiting, or for any other reason whatsoever, begins at the end of this time to become the victim of an acid intoxication, and unless something is done he becomes, in proportion to the intensity of this intoxication, a bad medical or surgical risk. The common notion that a few teaspoonfuls of glucose by rectum, a glass or two of milk, or a little gruel two or three times daily is all that the sick man needs, is something to be condemned thoroughly. Too often a persistent nausea and vomiting is the result of an acid intoxication, and maybe of the carbohydrate starvation type. One or two adequate carbohydrate administrations may "cure" such, but it is idle to think that a pint or two of a 2 per cent. glucose solution

by rectum will do it. One may begin with such childish measures, but unless some scheme is devised which will get several hundred grams of carbohydrate into such a patient, the therapy cannot be considered adequate. When, because of nausea and vomiting, the mouth route is not available, it is well to give glucose (dextrose) intravenously in sterile solution. For this purpose 50 or 100 grams ($1\frac{2}{3}$ or $3\frac{1}{4}$ ounces) may be given, in the form of a 25- to 30-per cent. solution, by slow intravenous injection. It is better to repeat such injection several times than give too large single doses. But as soon as the patient can be roused sufficiently to coöperate, a proper intake of carbohydrate by mouth presents the only adequate route. The patient should be offered materials rich in sugar, or other carbohydrates *which he likes*. Ice cream and fruit ices in large amounts do well; or orangeade sweetened with much milk sugar; or milk fortified with milk sugar; or good quantities of the different gruels. Iced tea or coffee carrying much milk sugar also do well. By the rectal or intravenous route, only that sugar is best used, of course, into which the body converts all the carbohydrates, namely, dextrose (glucose).

Tests for the Acetone Bodies.—With the above facts in mind, we may turn to the question of how best to discover any one of the three substances mentioned. Adequate for the purposes of the general practitioner, and easily performed, is Gerhardt's ferric chlorid test for diacetic acid.

To several c.c. of urine in a clean test tube there are added slowly several drops of a 10 per cent. solution of ferric chlorid. (If this is not available, the ordinary U. S. P. tincture of the chlorid of iron may be used.) The presence of diacetic acid betrays itself in the development of a burgundy red color.

In highly concentrated urine a whitish precipitate of phosphates may obscure the test. Under such circumstances it is well to take a fresh test tube and a new sample of the urine and dilute it strongly (with one or two volumes of water) before again adding the ferric chlorid.

The salicylates give a positive ferric chlorid test. Inquiry needs in consequence to be made of the patient as to whether he has previously taken sodium salicylate, oil of wintergreen, or such salicylic acid derivatives as salol, saliphen, aspirin, etc. Unless this is done a patient may be judged carbohydrate-starved when he is perfectly normal in this regard.

REDUCING SUBSTANCES IN THE URINE

(Sugar)

Fehling's Test.—While the reduction of an alkaline copper solution has many defects when used for the qualitative or quantitative estimation of sugar in the urine, it is so simple to execute that it will probably continue in clinical use indefinitely.

Of the available copper reduction tests, Fehling's is still the best and safest for qualitative work. For this two solutions are required, which should always be kept in well-stoppered dark bottles, and as separate solutions until the time of the actual performance of a test. The two solutions, which, if desired, may also be used for the quantitative estimation of sugar in the urine, have the following composition.

Solution I

Copper sulphate	34.639 grams
Distilled water, enough to make	500 c.c.

Solution II

Rochelle salts	173 grams
Potassium hydroxid	125 grams
Distilled water, enough to make	500 c.c.

When a test for sugar is to be performed, equal volumes of the two solutions are mixed in a test tube. The mixture should rise only to the height of an inch in the test tube. If the test is only for qualitative purposes it is well to see that an extra drop or two of the white alkaline solution is added, for urine, especially in diseased states, is often highly acid and it must be remembered that *in testing for sugar an alkaline medium is always necessary*. After the two solutions have been mixed, they should be heated to boiling in a test tube. This serves to show that the test solution itself is of good quality. If the pure test solution shows any change whatsoever from a brilliant blue, the stock reagents should be regarded with suspicion. If the mixture has remained a bright blue, five drops (*not more*) of the suspected urine are added to the test mixture and this is reheated. The presence of such a reducing sugar as dextrose manifests itself by yielding a red discoloration followed by the deposition of a red precipitate. For reasons which cannot be discussed in detail here* a yellowish precipitate may be obtained instead of a red one. At other times only a green or yellowish discoloration may result. It is generally said that these greenish or yellowish turbidities are of no significance. This is dangerous counsel, for while such may be the case, these greenish or yellowish discolorations may be as important as the most positive red precipitations. In such questionable cases it is well to do the test over again and in either of the following ways: If an immediate answer is needed, try the effects of adding ten or fifteen drops of the urine, or better, dilute the urine strongly with water and also dilute the copper test solution with an equal volume of water. If sugar is present, a definite red or yellow precipitate is almost sure to be obtained. If the result is still un-

*Refer to Bibliography, Hugh MacLean; Martin H. Fischer and Marian O. Hooker

satisfactory, mix equal volumes of the cold Fehling's solution with the cold urine and set the tube aside until the next day. If reducing bodies are present a red precipitate will fall out.

Two things happen which interfere with the accuracy of the Fehling test: There may, first of all, be substances present in the urine which, even though sugar is present, will not allow the red or yellow precipitate to form properly. Creatin, creatinin, and various hydrophilic colloids like the albumins, will thus interfere with the anticipated production of a yellow or red precipitate. But under these circumstances a sufficiently heavy dilution of the urine with water, or the carrying out of the test in the cold as described above, will usually suffice. Second, it must be remembered that the Fehling test is a general test for reducing substances. If any such are present, a positive reduction which may falsely lead to the belief that sugar is present may be obtained.

When formaldehyd is used to preserve urine, or when a formaldehyd derivative like hexamethylenamin is being given a patient (which leads to the excretion of formaldehyd in the urine), a positive reduction test is regularly to be expected, without this meaning, of course, that the patient is excreting sugar.

A next most important fact to remember is that the excretion of milk-sugar in the urine will also give a positive reduction test with Fehling's solution. Serious errors are made by not discovering that a positive reduction in a given specimen of urine is indicative, not of dextrose in the urine, but of lactose. Lactose commonly appears in the urine of women who are pregnant; it is not infrequent in lactating mothers and it is again very common when an infant is being weaned. It is to be expected, in other words, whenever the conditions are right for the absorption of milk-sugar from the breasts into the blood with which it is carried to the kidneys and excreted in the urine. A diagnosis of diabetes is all too commonly made upon such individuals, and this is then likely to be followed by the disastrous therapeutic suggestion of restricted carbohydrate intake. Such advice to a pregnant woman may be followed by the most serious consequences.

A third possibility for obtaining a positive reduction with Fehling's solution resides in the presence in the urine of materials like glycuronic acid, certain alkaloids, certain hypnotics (like chloral), the purin bases, and various albumins (which either contain a carbohydrate nucleus or a fraction which can be converted into carbohydrate). None of these substances, however, is likely to give as clean-cut and as positive a reduction, when the test is carried out as described above, as will sugar or the reducing substances previously discussed. A reduction is usually obtained only after larger quantities of urine have been used, after prolonged boiling of the test solution and usually not in such perfect form as in the case of sugar.

Mechanism of the Production of Sugar in the Urine.—Assuming that a qualitative analysis, with due regard to its possible errors, has led to the conclusion that sugar is present in the urine, what is its significance

for the patient? To understand this properly the general physiology of carbohydrate chemistry in the body must be understood.

The presence of dextrose in the urine (glycosuria) is so greatly the predominating sign of a diabetes mellitus that a brief study of the mechanism by which this is brought about may well be regarded as a prerequisite to an intelligent understanding of the disease itself. We must, therefore, first inquire as to what are the circumstances under which we may find dextrose in the urine. So far as human beings are concerned, and most animals, there can be no doubt that sugar is always present in traces in the urine of even entirely normal individuals. But this amount of sugar is too small to be recognized save by expert chemical means and has from the standpoint of the physiology of glycosuria more a theoretical than a practical interest.

By the term "glycosuria" we ordinarily mean only the increase in amount of dextrose in the urine above this trifling normal. What are the causes that lead to such a glycosuria? While, as we shall see, these may be many and various, they can all be grouped under two classes, namely, such as are said to lead to an "increased permeability" of the kidney cells to dextrose, and second, such as increase the concentration of this sugar in the circulating blood. The circulating blood always contains some dextrose, but its percentage, while subject to considerable variations, at no time normally exceeds (about) 0.2 per cent. When the concentration of sugar in the blood exceeds this value, the kidney cells are unable to hold it back, and some of it goes over into the urine. The same end is accomplished when, instead of raising the percentage of sugar in the blood, the permeability of the kidney cells is increased so that sugar may go over into the urine even when present in less than 0.2 per cent. in the blood.

Let us now consider these two types in somewhat greater detail.

(1) *The Glycosurias Not Associated with an Increase in the Concentration of Sugar in the Blood.*—Under this heading fall the renal diabetes, of which, so far as I know, only three experimental forms exist. The first of these is *phlorizin glycosuria*. If this substance is introduced intravenously, subcutaneously, or *per os* into any animal, there follows an excretion of dextrose in the urine within a few hours after its administration and this continues from one to several days, ceasing only when all of the poison has been eliminated or when all the sugar has disappeared from the body of the animal. During the entire time of the glycosuria no increase in the concentration of sugar in the blood is noted. This type of glycosuria is of clinical importance only in connection with some of the older kidney function tests when phlorizin would be administered to human beings.

Such an increase in the permeability of the kidneys to sugar is observed also after the *intravenous injection of pure sodium chlorid* and various other salt solutions into animals or man. Since such a temporary glycosuria may be observed clinically it must be kept in mind. A third experimental form is said to accompany the increased urinary flow following the administration of *caffein*, *theobromin* and

diuretin. It may be observed clinically, but being transient in type, is of little significance if only its true nature is recognized.

Glycosurias, unassociated with an increase in the concentration of the blood-sugar above the normal maximum, have been described in man and they have on this ground been diagnosed as renal diabetes, but up to the present time there seems to be little evidence to sustain the belief that the described clinical cases are not such as have merely complicated rather than followed upon any recognizable kidney lesions.

(2) *The Glycosurias Associated with an Increase in the Concentration of Sugar in the Blood.*—Under this heading fall the majority of the experimental glycosurias, and all the clinical forms, excepting those following phlorizin administration. It is well to begin consideration of this group by referring to the glycosuria which follows the ingestion of excessive amounts of carbohydrate. Generally speaking, every animal can be made to excrete sugar in the urine if only sufficient carbohydrate is consumed in a sufficiently short period of time. Under such circumstances there is rapid absorption of sugar with rapid increase in the concentration of the blood going to the liver. If the increase exceeds the capacity of the liver for converting this sugar into glycogen, and thus storing it, the sugar passes on into the general circulation where, if its concentration exceeds 0.2 per cent., its elimination into the urine begins. Furthermore, when fed in excessive amounts the usual road of absorption for sugar through the blood may be augmented by a direct absorption more especially from the lower portion of the small intestine into the lymph, and through the thoracic duct into the general circulation from which the kidneys are then reached more directly.

It is clear that a number of factors play a rôle in bringing about such an "alimentary glycosuria," among which need only to be mentioned the rate of feeding, the amount of feeding, the kind of carbohydrate fed, the rate of absorption, the region of absorption, the amount of sugar already in the blood, the condition of the liver and muscles so far as their powers of changing sugar to glycogen and their store of glycogen are concerned, and the state of the kidneys. It will, therefore, not seem strange that the "toleration limit" for carbohydrates is different, not only in different individuals, but in the same individual under different circumstances. We see also how through pathological states of the most varied kinds, what may be called the normal toleration limit of an individual can be markedly decreased or increased.

With these remarks concerning a "physiological" glycosuria, we may pass to a more pathological type, namely, that which follows puncture of the floor of the fourth ventricle. Shortly after such injury the per cent. of dextrose in the blood begins to rise, and usually within an hour sugar appears in the urine. This excretion of sugar may continue for several days, at the end of which time the liver is found (practically) free from glycogen and sugar. This type of glycosuria may be seen clinically after injury to the central nervous system, as after

accidents to the head or the pathological consequences of tumors, syphilis, etc.

Instead of injuring the medulla directly, it is possible to affect this indirectly and so bring about a glycosuria. Two roads are open for this, namely, the nervous and the circulatory systems. Stimulation of the central end of practically any of the afferent nerves is followed by glycosuria. As the more striking examples we need only mention the sciatic, the vagus and the trifacial. It has been thought that some of the transient glycosurias following painful injuries of the peripheral nerves in human beings belong in this class.

A number of substances which may be injected into the blood are capable of affecting the medulla and bringing about a glycosuria. The *chlorid, iodid, bromid and nitrate of sodium, lithium, potassium or strontium* at suitable concentration, are all effective in this regard. Into this same group with the salts may be put the acids (lactic, phosphoric, sulphuric, hydrochloric, etc.) which have been found capable of inducing a glycosuria.

The glycosuria which follows *lack of oxygen*, or any condition which in its ultimate analysis leads to a lack of oxygen, such as poisoning by carbon monoxid, curare, strychnin or tetanus toxin, must be considered under this heading, for we know that as a result of lack of oxygen, various acids and other poisonous substances are produced in the tissues which we have no reason to consider act differently from the salts or acids that are introduced indirectly from without.

Various *anesthetics* are also capable of producing a glycosuria. Chloroform and ether constitute common examples, and morphin and chloral with their many derivatives act similarly. Clinical illustrations of glycosuria following the administration of these substances are not uncommon.

The *pancreatic form* of glycosuria constitutes another example of the class which is associated with an increase in the concentration of sugar in the blood. If the pancreas is entirely removed from an animal, an excretion of sugar in the urine begins within a few hours. The glycosuria brought about by this means is the most intense of the experimental types and is associated with all the signs and symptoms which are characteristic of the severest diabetes in human beings. The excretion of sugar is not due to a lack of the pancreatic enzymes in the intestinal lumen, for simple ligation of the pancreatic ducts is not followed by glycosuria. Nor does glycosuria result if the entire gland is extirpated, but a piece is transplanted under the skin. If this piece is removed, sugar promptly appears in the urine. The facts are explained by saying that the pancreas gives off an internal secretion to the blood, the presence of which is necessary for a proper carbohydrate metabolism, but the nature of this relation of an unknown constituent of the pancreas to carbohydrate metabolism is not yet understood.

With pancreatic glycosuria we have to consider the glycosuria which follows the *intravenous injection of adrenalin*. This substance seems to owe its effect to an action upon the pancreas. When applied locally to

this organ a glycosuria results. With adrenalin may be classed a long series of other chemicals (such as the cyanids) which have nothing in common with adrenalin excepting a reducing action.

A last (as yet not well established) form of glycosuria is the *hepatic*. The injection of ether and certain other substances into the portal vein is followed by the appearance of sugar in the urine. The hepatic form of glycosuria has been held to find a parallel in the glycosurias found associated at times with liver cirrhoses.

The foregoing paragraphs have considered only those measures which have been found experimentally to produce glycosuria and for which clinical analogies have been discovered with fair certainty. It must be clear to every one, however, that these in no sense constitute *all* the possible disturbances which may be imagined capable of so interfering with the consumption, absorption, storage, utilization or elimination of the various carbohydrates as to lead to a glycosuria.

Diabetes Mellitus.—Of the various glycosurias which have been discussed the physician takes special interest in the *persistent* types, for it is the persistency of a glycosuria which leads in ordinary practice to the diagnosis of diabetes mellitus. While it is obvious that such a diabetes mellitus may clinically be due to disease of very different organs (as of the pancreas, of the brain, or of the liver), it is generally accepted that most are of the pancreatic type. Sometimes the severer grades of diabetes are alone attributed to disease of the pancreas and the milder ones to disease elsewhere in the body. The first half of this conclusion is undoubtedly correct in essence, but the second half need not be. There are undoubtedly mild cases of pancreatic diabetes. Neither is it correct to assume that a *transient* (say, one lasting some days or a few weeks) glycosuria cannot have been pancreatic in type. We are still largely ignorant of what nature of pathological change in the pancreas leads to a destruction of its function of internal secretion; but obviously such a change must have a beginning and, also, it need not necessarily be irreversible. Only in the latter instance does a disappearance of the glycosuria after once being established become impossible.*

Since an analysis of the urine is constantly used to cheer or discourage the diabetic under our care, it is well to know just which

*It is the author's opinion that an intoxication of the pancreas due to a soluble poison of some sort or one derived from a direct or metastatic infection of the pancreas by a pus organism or syphilis, may so interfere with the internal secretion of this organ as to lead to a glycosuria. This idea was first suggested to the writer by R. T. Woodyatt, but whether he still holds to it, the writer does not know. Syphilitic changes in the pancreas of diabetics have been described by A. S. Warthin. The author has seen most violent types of glycosuria develop suddenly in patients with acute tonsillitis, acute alveolar abscesses, and active syphilitic infections. The alleged variations in "tolerance" in diabetics have seemed to the author to be more logically explainable on the basis of new infections or recrudescences in old ones than on any other. Practically, the author has found that those diabetics who are not already in the "severe" class (see below) fail to get worse, and often show decided increase in tolerance if they will submit to a surgical cleaning up of all points of infection (in teeth, tonsils, sinuses, hemorrhoids, prostates, toe-nails, gall-bladders, etc.) or allow themselves to be properly treated for syphilis.

features of it are important, and which are not. But to do this some primary principles regarding carbohydrate chemistry must be carried in mind.

Judging the Glycosuric Individual.—Altogether too much attention is paid to the problem of the percentage of sugar which a given patient eliminates. It must be clear to any one that, so far as amount of sugar excretion is concerned, a patient who excretes two liters of urine containing 1 per cent. of reducing substance is no worse off than another excreting four liters containing one-half per cent. From a quantitative point of view, sugar estimations should, in other words, consider not only the concentration of the sugar, but the total amount of urine put out in each twenty-four hours. The percentage concentration should always be multiplied by the amount of urine voided in the twenty-four-hour period.

But even when correctly estimated, this figure, too, is of little or no importance. The really important thing for the diabetic is not the percentage or amount of carbohydrate which he loses every day, but the amount which he can use before losing any. It is this which is the measure of his *tolerance*, and to discover what this is we must know the quantitative and qualitative nature of his food intake.

Unless there are indications to the contrary, a good index to tolerance may be obtained by any physician by simply placing his patient at bed-rest and upon a carbohydrate-free diet.* For practical purposes this amounts to starvation for three days, the patient being allowed only such materials as coffee, consommé, some green salad, skim milk cheese, etc., as the ingenuity of the physician may dictate. In patients who are the victims of only a mild or a moderately severe degree of diabetes, such restriction in diet will not only reduce markedly the presence of sugar in the urine but in the milder cases will make it disappear entirely. Often twenty-four hours of such restriction suffice to clear the urine. If the sugar has not disappeared completely by the end of the third day the experiment may be continued one more twenty-four-hour period, but it has been the writer's experience that there is little use in pressing the starvation beyond this point.

If the patient is of the fortunate group which clears completely, we may discover how much carbohydrate he is able to utilize in each twenty-four hours by adding to the established ground diet increasingly greater and measured amounts of some carbohydrate (like white bread)

* Some care is necessary in doing this, as the further discussion will show. Before beginning with a carbohydrate-free diet, it is well to keep the patient on his accustomed diet and test the urine for acetone compounds. If they are absent, the carbohydrate-free diet may be started at once. If present, begin by cutting all fats from the dietary. If the acetone compounds disappear after a few days, the carbohydrate-free diet may be begun. If they do not disappear the patient is probably fat or in the class of the severer diabetics, and if the carbohydrate free diet is then tried the possibilities for seeing the development of coma must be kept in mind and measures taken to forestall possible bad effects (through alkalization, the administration of magnesium sulphate, or of calcium salts, preparation for intravenous dextrose injections, etc.)

until the sugar reappears in the urine. We may then use this figure to indicate the patient's tolerance at the time and to guide us in prescribing for him a proper diet. In the hope of resting or "sparing" these organs which have to do with carbohydrate metabolism and which are defective in the case of the diabetic the patient is ordinarily advised to live on a diet which will keep him sugar-free, and at longer or shorter intervals this carbohydrate ration is cut down still more in order further to rest his diseased pancreas or other organ. While such treatment may find scientific justification in the case of newly developed and acute glycosurias, considerable evidence may be brought forward to show that such drastic revision may not only not benefit, but actually does harm in the established, more chronic diabetic. In these the writer has long given carbohydrate *just to the point where a little sugar appears in the urine*. On the whole, the author's opinion is that it is safer to err on the side of giving a little more than enough carbohydrate, than to give too little.

These suggestions regarding carbohydrate feeding are so unorthodox that they require justification. Briefly, the reasons therefore may be presented as follows: In the established chronic diabetic all evidence seems to indicate that the tolerance of the individual to carbohydrate can not be changed through mere decreases in the carbohydrate ration itself. While after a prolonged fast a patient may show an increased tolerance, this increase is, the author believes, more often imagined than real. When through prolonged fasting the carbohydrate depots of the body have been exhausted, a little time is required after carbohydrate feeding is recommenced to replenish these depots, and during this time the patient shows an apparent increase in his carbohydrate tolerance.

It is an easy matter to become unduly impressed by the percentages or total amounts of sugar which a diabetic may throw off in the urine. It is well to understand what such a sugar loss means to the diabetic. Excepting in the severest types of diabetes, it is not this loss of sugar which kills the patient. While it does, of course, represent a food loss which must be subtracted from his total food intake, it does not become a killing element unless the "tolerance" (which represents how much carbohydrate is used before any is thrown out) is so low as to compel the patient to live on his own tissues. The presence of an overplus of sugar in the tissues dehydrates these and gives the patient thirst. To satisfy this he drinks a more than usual amount of water and thus his urinary excretion of water goes up. Too great freedom in carbohydrate feeding will, therefore, increase the thirst and the frequency of urination in a diabetic, but these are not killing things. *It is the amount of sugar that can be used by the organism before any sugar appears in the urine that is of importance, for, generally speaking, all sugar consumed beyond this toleration limit will be excreted.* What kills the diabetic, however, is not the effect of such excessive amounts of sugar in the tissues or of the loss of a certain amount of sugar in the urine, except as these are accompanied by so low a carbohydrate tolerance

that the patient is starved. What kills the diabetic even in the severer cases is not his starvation, but *the intoxication with acetone, diacetic acid and beta-oxybutyric acid formed in consequence of an inadequate and improper oxidation of the fats* due to the fact that an inadequate amount of carbohydrate is being burned on a too large ration of fat is being fed.

It is for this reason that the dietary regimen of the diabetic calls also for a decided revision downwards of the fat intake and for a more or less active administration of alkalis. The fat restriction makes not only for a reduction in the production of the acetone bodies, but the consistent and persistent feeding of alkalis tends to neutralize the acidic acetone bodies as formed and thus to reduce their effects upon the organism. But such neutralization in its turn improves the powers of the organism to use carbohydrate which is always reduced when the acid-content of living cells is increased. In this way another factor enters the field to aid further the carbohydrate tolerance.

All these things may be accomplished with relative ease in the milder diabetics, the difficulties growing with every increase in the lower tolerance for carbohydrate of the individual until in the severest forms (the absolute diabetic) the difficulties are practically insuperable. The absolute diabetic, for instance, uses none of the carbohydrate fed him and converts 60 per cent. of his protein into sugar and throws this off.* He lives, in consequence, upon only 40 per cent. of his protein and upon such fat as he may be able to use. But even this fat ceases to burn properly, yielding in large measure the acetone compounds. So far as these may be acid in type (like beta-oxybutyric and diacetic acids) they can still be neutralized by giving alkali, but acetone cannot be gotten rid of in this fashion. Since acetone is a typical anesthetic, the diabetic tends literally to become anesthetized to death. Failure, of course, to heed any of the other principles which have been laid down only hastens this end. The diabetic tends from the first to die of partial starvation, to which are then added the effects of an acid intoxication if insufficient alkali is fed, while in the severer cases the direct anesthesia due to acetone and like compounds is superimposed.

Guided by the facts brought out above and on the basis of personal experience, the rules for the treatment of a diabetic may therefore be summarized as follows:

1. Feed carbohydrate at least to the point where a little sugar is constantly present in the urine.
2. Reduce the fat ration completely at first to get rid, if possible, of all acetone compounds. When fat feeding is resumed, do not allow this fraction of the diet to exceed an amount which can be burned to carbon dioxide and water in the presence of the amount of carbohydrate for which the patient still has a tolerance.
3. Give enough alkali, preferably in the form of a mixture of

* See Graham Lusk: *Science of Nutrition*, 2d Edition, W. B. Saunders Company, Philadelphia, 1917, p. 207.

several alkaline salts,* to keep the urine constantly neutral to litmus, or constantly alkaline to methyl red.

An index to the effectiveness of such therapy may be found in the urine in the form of a lowered water output, a lowered sugar content, a diminution in the acetone compounds excreted and in a persistently neutral reaction of the urine. But this is not all that must guide the physician. The patient (after losing, perhaps, his excessive fat deposits) must maintain his weight, he must show an improvement in his sensation of lassitude, and his thirst and polyuria must be under better control. There is such a thing as a satisfactory urinalysis and a life not worth living. There are times when, if necessary, it may be better to die a little sooner and comfortably than to exist longer, miserably.

PROTEINS IN THE URINE

(Albuminuria)

Qualitative Tests for Protein.—In making the qualitative tests for protein it is necessary to have the urine as clear as possible and of a slightly acid reaction. If the urine is not clear it should be filtered carefully through a sheet of moistened filter paper. Traces of albumin may be missed in urine which is even slightly turbid. If the urine is not distinctly acid to litmus paper, a drop or two of 5 per cent. acetic acid should be added to a small portion (like 10 c.c.) of the urine. Care should be taken not to add too much acid. The ordinary albumin reactions also require for their proper development the presence of neutral salts. It is ordinarily taken for granted that these are contained in sufficient amount in the sample to be tested, but this is dangerous at times, especially in urines of low specific gravity or of high acidity. If there is any doubt in the matter two or three drops of a saturated sodium chlorid solution should be added to the sample to be tested.

* The continuous production of fixed acids in the body, with its consequent continued call upon the reserve of fixed alkalies, exhausts not only the sodium and potassium salts, but also the more important calcium, magnesium, and iron salts. It is easy enough to replace the sodium salt by feeding baking soda, but this does not make up for the loss of other salts. An excellent source of alkali is found in the vegetables, but when these have been boiled several times to deprive them of soluble carbohydrates, they have also been much depleted in their different salts. It is for this reason that the writer has long used in all the acid intoxications, including diabetes, the following mixture:

Sodium bicarbonate	100 grams (3½ ounces)
Precipitated calcium carbonate	50 grams (1½ ounces)
Magnesium oxid	50 grams (1½ ounces)

(or
call
but
urine)

produces too much cathartic action, and if
If thought necessary other salts may be added like pc
hydroxid, etc.

The best qualitative test for protein in the urine is *Heller's cold nitric acid test*, which should be performed as follows: Pour the clear or filtered specimen of urine into a clean test tube to the height of an inch. Make sure that the urine is acid by testing with litmus paper. If necessary, add one or two drops of 5 per cent. acetic acid. Take up 5 c.c. of concentrated nitric acid into a volumetric or other pipette and, holding the test tube with its content of urine in an almost horizontal position, allow the nitric acid to flow down the side of the test tube *as slowly as possible*, to form a sharply defined layer below the urine. The manipulation must be made without getting the two liquids mixed with each other.

The development of a white ring varying in intensity from a bare cloudiness to a curd-like disc at the point of contact of nitric acid with urine indicates the presence of protein. Mere changes in color are not significant. Turbidities at some distance above the line of contact between acid and urine are not to be considered as indicative of albuminuria. They are usually mucin rings or precipitated urates.

Care is necessary in applying the nitric acid test to urine which is too highly concentrated. Under such circumstances the addition of nitric acid leads to the formation of urea nitrate which may form a ring at the point of contact of acid and urine, but the fact that the ring no longer appears if the test is repeated with diluted urine, and the distinctly crystalline character of the ring, serve to distinguish it from a protein reaction. If the patient is taking any of the aromatic oils, like santal oil, balsam of copaiba, or balsam of tolu, what looks like an albumin reaction may be obtained. Such a ring is, of course, of no significance and its true import is at once clear if the patient is asked regarding any drugs he may be taking.

A second popular test for protein in the urine is the *heat test*. The possibilities for error are, however, greater with this test than with the cold nitric acid test. In applying the heat test the following rules must be strictly adhered to: The urine must be absolutely clear and have enough acetic acid added to it to give a distinctly acid reaction with litmus. If there is doubt as to the amount of salt in the urine two or three drops of concentrated sodium-chlorid solution should be added. A clean test tube is filled to within an inch of the top with this urine, and the upper half of the fluid column is heated to the boiling point. Care should be taken not to have the urine boil over and soil the outside of the test tube. The appearance of a turbidity in the boiled section of the urine is indicative of the presence of protein. To make sure of the matter, however, and to distinguish it from a precipitate of phosphates, two or three drops of concentrated nitric acid should be dropped upon the turbid column of urine. If the turbidity clears, it is *not* due to albumin, but if the turbidity remains or increases in intensity, it is safe to consider the reaction as positive for protein.

Quantitative Estimations of Protein.—Quantitative estimations of the amount of protein in the urine are not of much significance to the general practitioner. It is enough, ordinarily, to say that the protein

is present in small, medium or large amounts. If, however, it is desired to make more accurate determinations, the *Esbach test* as modified by Tsuchiya is the best to use. In the original Esbach method a specially graduated test tube is first filled with urine to a given mark, and upon this is then poured, to another given mark, Esbach's solution, the formula of which is as follows:

Picric acid	10 grams
Citric acid	20 grams
Distilled water, enough to make.....	1,000 c.c.

The test tube is inverted several times to assure perfect mixing of reagent and urine, and the whole is then set aside in a vertical position for twenty-four hours. The amount of albumin is read off directly in grams per liter of urine from the scale at the side of the test tube.

In *Tsuchiya's modification of the Esbach method* the procedure is the same, only instead of Esbach's reagent the following is used:

Phosphotungstic acid	1.5 grams
Concentrated hydrochloric acid	5 c.c.
Alcohol, enough to make	100 c.c.

With Tsuchiya's reagent the precipitate forms more quickly, is of higher specific gravity and settles out more satisfactorily.

Various factors influence the accuracy of the quantitative results obtained, but this Esbach method suffices for all ordinary purposes. Neither the original Esbach nor the modified method must be used for the *qualitative* recognition of albumin, because other things than protein are thrown down both by Esbach's and Tsuchiya's reagents. In making quantitative albumin tests, it is well also to precede these by measuring the specific gravity of the urine. It should not exceed 1.010, for the higher the specific gravity of the urine the less easily does the protein precipitate settle down, which, in consequence, leads to the assumption that more protein is present than is really the case. The method becomes fallacious also if the amount of protein in the urine is very high (over six or seven grams per liter). Under such circumstances it is well to dilute the urine a known amount, run a second test, and multiply the result thus obtained by the degree of dilution.

Origin of Urinary Protein.—The finding of protein in the urine is to be taken as an indication of a destructive lesion somewhere in the genito-urinary tract. The position and nature of the destructive lesion needs then to be determined. But for purposes of diagnosis, prognosis and treatment it is also necessary to know how these destructive lesions come to contribute to the presence of protein in the urine. Very commonly, as we shall see, the first cause of an albuminuria may lie entirely outside of the genito-urinary tract itself.

A useful first differentiation needs to be made between lesions in the kidney itself and all lesions below this point (pyelitis, ureteral stone,

cystitis, urethritis). Neither qualitative nor quantitative protein analyses help much in this regard. Pure kidney lesions may yield several grams of albumin to the liter of urine, and pure lesions lower down may yield only traces. On the other hand, all the alleged tests for "specific" albumins coming from kidney, bladder or elsewhere are, even in experts' hands, full of fallacies.

Microscopic search for casts (*see* below) is the best one method of determining whether the kidney is involved. When casts are found it is safe to assume that there is a definite lesion in the kidney. This method of differential diagnosis fails only if the patient is voiding a definitely alkaline urine. Whether such alkalinity be due to the administration of alkalies or to ammoniacal decomposition, the result is the same—casts, even though present, are likely to be "dissolved." Persistent absence of casts from all urines excepting those which are alkaline may be taken as sound evidence for the existence of no lesion in the kidney. The albumin under these circumstances comes from somewhere below the kidney parenchyma. From just where must be determined by other accessory methods of examination such as palpation of the kidneys or bladder, digital examination of the prostate and seminal vesicles, inspection of the urethra, x-ray examination of the kidney pelves and ureters, cystoscopic examination of the bladder, ureteral catheterization, etc.

Barring the possibility previously noted of bacteria synthesizing protein from urea and other nitrogenous compounds formed in the urine—a possibility largely negligible if only freshly voided samples are examined—the presence of protein in the urine is always to be regarded as due to a "solution" phenomenon somewhere in the genito-urinary tract. In consequence of the action of any noxious agent (like a poison or a group of bacteria), living cells anywhere in the genito-urinary tract may begin to swell, to show fatty degeneration and, if the noxious agent acts severely and long enough, to necrose. As these changes occur, protein in increasing amount begins to "dissolve" in the urine which bathes the lesion. A first source of albumin in urine is, therefore, to be found in the direct solution of all or a part of the cells found somewhere in the genito-urinary tract over which the urine washes. Obviously also, other things being equal, the amount of protein which will appear in the urine will be an index to the amount of genito-urinary protoplasm which is suffering destruction.

A second source of albumin is found in connection with the hemorrhages incident to genito-urinary lesions. Not only may a destructive lesion directly erode the walls of smaller or larger blood-vessels and so give rise to direct hemorrhage, but red blood-corpuscles may also migrate (by diapedesis) through the softened blood-vessel walls and genito-urinary tissues and so get into the urine. Acid or alkaline urine, or urine low in salts will then make these corpuscles lose their hemoglobin or dissolve entirely. Either process leads to the development of a positive protein reaction in the urine. Needless to add, the grosser hemorrhages allow not only the red blood-corpuscles to escape through the

blood-vessels and into the urine; but the plasma of the blood as well. This furnishes an additional source of albumin.

The third source of albumin is found in the solution of white blood-corpuscles in the urine. The white blood-corpuscles are to the front whenever the destructive lesion in the genito-urinary system is of the ordinary acute inflammatory type. The presence of many white cells and of much albumin derived from such is, therefore, always strongly suggestive of infection as responsible for the observed kidney or other genito-urinary lesion (infectious nephritis, pyelitis, cystitis, urethritis as due, for example, to streptococci, staphylococci or gonococci).

The Albuminuria of "Nephritis."—Having determined that protein is present in the urine, and having decided by other methods of investigation that the lesion lies in a kidney, somewhere below the kidney, or in both these places, we need next to determine its significance from a prognostic point of view for the patient. As every one knows, there exist marked albuminurias which somehow or other fail to injure a patient, while on the other hand there may appear only traces of albumin, and these perhaps only at times, which all too often are associated with the death of the victim.

There is generally not much difficulty in coming to a correct decision in lesions *below* the kidney. A pyelitis, cystitis or urethritis is usually rated as severe or as mild, gets worse or better in proportion to the urinary findings. We shall, in consequence, not pursue this question further. But no such simple relation seems to exist in the case of pure kidney lesions where it is seen that complete suppression of urine, with great quantities of albumin in such as may have been voided just before the suppression began, may be followed by no "uremic" symptoms whatsoever, while in other patients with mere traces of albumin, death in coma follows.

Actually, such difficulties in prognosis do not exist. They seem to, only because wrong interpretations and wrong deductions are made from the urinary findings. It is not only important to know what conclusions *may* be drawn from a proper urinary analysis, but *which may not be drawn*. More mistakes are made under the second heading than under the first. To get the matter clear in mind some introductory remarks on the nature, cause and classification of the nephritides are necessary.

The term nephritis is here used in its accepted clinical meaning as covering that symptom-complex which is characterized by the appearance of albumin in the urine in association with casts, by quantitative variations in the amount of urine secreted, by quantitative variations in the amounts of dissolved substances secreted, etc.

In order not to confuse things, it is well to consider first those nephritides which follow, for example, any general intoxication of the kidney, as such which follow bichlorid-poisoning, intoxication with a soluble bacterial toxin, etc. Under such circumstances there results a so-called "generalized parenchymatous nephritis." Where belong the other types of nephritis (as, for example, the chronic interstitial type

associated with a cardiac hypertrophy and high blood-pressure) we shall see later.

All the changes that characterize nephritis are colloid-chemical in nature and are produced through changes in the colloids making up the kidney. As of first importance in bringing about these colloid-chemical changes, there is to be counted an abnormal production or accumulation in the kidney of acids and of certain other substances which in their action upon colloids behave like acids. In the latter group are found pyridin, urea and various amins, the latter having much in common with the toxins of the infectious diseases, some of which are also amins.

The correctness of these conclusions has been verified in many directions by showing: (1) that there is evidence in every case of nephritis of an abnormal production and accumulation of acids and similarly acting substances in the cells of the kidney; (2) that any method by which such an abnormal production and accumulation of these substances may be brought about in the kidney results in the signs and symptoms characteristic of nephritis; and (3) that with these ideas in mind much can be done clinically in "nephritis" to relieve the clinical signs and symptoms characteristic of this "disease."

The item under the first of these three headings which is of great importance in urinalysis is that the acidity of the urine (*see above*) generally runs high in nephritis. Under the second heading, namely, that any scheme which results in an abnormal production and accumulation of acid (and similarly acting substances) in the cells of the kidney is followed by the signs and symptoms of nephritis, we again discover a series of facts of great clinical importance, for what we call the "causes" of nephritis are only such things as lead to an abnormal production and accumulation of acid (and of like substances) in the kidney. Since, in the matter of treatment, the physician finds it necessary to be cognizant of and to remove as many of such features as he can, it behooves him to get them clearly in mind.

The quickest way in which to increase the acid content of the kidney is to inject acid intravenously. When this is done, we find that the animal thus experimented upon begins to show a decrease in urinary output, which may go to the point of complete suppression, while such urine as is secreted is not only highly acid, but charged with albumin, blood, and casts. At the same time, the animal begins to retain the water that is being injected along with the acid, and so develops a generalized edema. In other words, the animal shows all the signs and symptoms of a so-called "parenchymatous nephritis."

It will at once be interposed that this may be important from an experimental point of view, but that it has nothing to do with the practical problems of everyday medicine. But it has. We produce, even normally, enormous quantities of acids in our bodies in the course of our ordinary metabolism. The amount and rate of production of this acid can, however, be greatly increased at will. Whenever our muscles contract, they do so by reason of a production of acids (chiefly

lactic acid) in them. When we exercise quietly, the oxidation of these acids follows rapidly; so they never accumulate to any extent in the muscles. But in athletic endeavors of various sorts (rowing, running, basket-ball matches, etc.) the rate at which the acid is produced is enormously increased. The respiration and circulation become accelerated in an effort to supply the organism with sufficient oxygen to oxidize the increased amount of acid thus produced. But if the work is carried to the point of dyspnea, it means that, in spite of the increased cardiac and respiratory activity, the organism is no longer succeeding in the attempt. The lactic acid, therefore, begins to spill over from the muscles into the general circulation, and by this is carried to the kidney. Under these circumstances albumin and casts appear in the urine. It might be thought that such hard athletic games occasionally yield a little albumin; the fact, however, is that they yield not a little, but a great deal. After hard athletic endeavors, athletes may show several grams of albumin in the liter of urine, and such quantities of casts as are seen ordinarily only in examining the urines of the acutest "nephritics."

The real reason why the athlete shows albumin and casts is because his respiratory and cardiac activity are inadequate, during the times of great acid production in the body, to furnish sufficient oxygen to oxidize the acid so formed. But, as stated before, we need a good circulation and respiration even to oxidize those quantities of acids which are produced when the organism is in a state of comparative rest. This explains why, in the quiescent individual when the circulation becomes embarrassed (as in heart disease) or when the respiration becomes interfered with (as from a pleurisy with effusion) the acid accumulation in the body mounts; and as this acid accumulation makes itself felt in the kidney, albumin (and casts) appear in the urine.

But even if we do not interfere with the heart's activity or the respiratory activity, but interfere with the oxygen-carrying power of the blood, as through anemia or carbon-monoxid poisoning, we shall then also get this disproportion between the rate of acid production in the body and its proper oxidation, which again results in an abnormal accumulation of acid in the kidney, and, therefore, in the albuminuria and casts so common in these conditions. A lowering of body temperature, as incident to exposure to great cold, also brings about this result.

It should be observed that all these conditions leading to nephritis lie, in the main, *entirely outside the kidney*. The writer emphasizes this because all such extrarenal factors must be discovered and removed as far as possible whenever we try to discover the import of, or the cause for, an albuminuria, or try to relieve it. But any cause which will interfere directly or indirectly with the normal oxidation chemistry of the kidney cells themselves will lead to the appearance of albumin in the urine. For this reason tumors pressing upon the afferent or efferent blood-vessels of the kidney, or an arteriosclerosis involving the whole or pieces of the kidney, a thrombosis, an embolism, or similar disturbances, all result

in the appearance of albumin (and casts) in the urine. Or, without interfering with the circulation of blood into or through the kidney directly, we may make it impossible for this organ to use the oxygen which is brought to it. We shall, then, again have an abnormal production and accumulation of acid in the kidney. Thus it comes about that a kidney is poisoned and albuminuria results whenever this organ is bathed in the toxins of an infectious disease, is poisoned with chloroform, ether, or alcohol, with arsenic, uranium, chromium, or lead, or with such substances as phosphorus or the nitrites.

The acids (and similarly acting substances) which in their action upon the kidney lead to the various signs characteristic of this pathological condition do this about as follows:

The kidney is composed of a series of colloids. Those which interest us most and make up the bulk of the kidney are the protein colloids.

When any protein colloid (such as fibrin) is placed in a neutral solution (water), it swells somewhat. This is analogous to the normal state of the kidney. If a little acid is added to the water containing the fibrin, it swells much more. This is analogous to the enlargement of the kidney in nephritis (edema of the kidney). But, at the same time that the fibrin swells in this way, it also tends to go into solution. This is analogous to the going into solution of the kidney substance in nephritis—in other words, to the albuminuria.

Under the influence of the acid, the kidney also falls apart into its morphological constituents. The epithelial cells stick together and loosen in mass as the cement substances that bind the kidney structures together “dissolve.” This marks the origin of the epithelial cast. By more prolonged action of the acid or with a rise in its concentration, the epithelial casts are converted into granular casts, and, later still, into hyaline casts.

What has been said covers the essential elements of that which constitutes the picture of what is commonly called “acute” or “generalized” parenchymatous nephritis. But there exist also chronic types of nephritis, and some of these show high blood-pressure, cardiac hypertrophy, etc. What is the relation between the varying urinary findings discoverable in all such instances and the state of the kidneys? What is the significance of much or little albumin, and what does it mean for prognosis? To understand matters aright, a classification of the nephritides must be attempted, and later the relation between kidney disease and its alleged consequences be taken up.

There is really only one type of nephritis—parenchymatous nephritis. There is, however, a difference in the amount of kidney substance that may be involved. It is well to distinguish between *generalized* and *focal nephritis*. *It is in the generalized type that we observe the greatest decrease in urinary output, the most highly concentrated and most highly acid urine, the greatest amount of albumin, and the largest number of casts.* Conversely, such findings in the urine mean great and general involvement of the kidney. When only smaller parts of the kidney are

involved, all these signs are proportionately less. The first type of nephritis is found in cases of general intoxication, as in scarlet fever or in carbon-monoxid poisoning, after an anesthetic, or in the more chronic types of poisoning, as with phosphorus, mercury or lead. If larger or smaller pieces of a kidney thus affected die and the defect is replaced by connective tissue, the kidney substance is reduced in amount and we find on autopsy the so-called "*secondarily contracted kidney*"—one type, in other words, of the so-called "*chronic interstitial nephritis*." But it must be remembered that as long as one-fourth of the total kidney substance which a normal animal or human being has, is left intact, the animal (or patient) may be unaware of the fact that he has kidney disease, for even less than this amount is adequate for all ordinary demands. Neither does such an animal (or patient) show any increased blood-pressure, cardiac hypertrophy, uremia, or any other of the alleged consequences of kidney disease. He may live and die without being aware of his kidney condition, and we have at the present no way of diagnosing such a state before death. Calling to mind what was written above, it may be said that a patient's water output is an index to the amount of his kidney still functioning and not ill; his albumin and cast output an index to the amount of kidney which is involved and ill.

In the commoner types of chronic interstitial nephritis which we find in association with blood-vessel disease, heart hypertrophy and high blood-pressure (the so-called "*primarily contracted kidney*"), we also deal with a gradually progressing focal destruction of kidney substance. The primary change in this condition is not kidney disease, however, but blood-vessel disease; and the general signs observable in such a patient are primarily not due to defective elimination of poison through the partially destroyed kidneys, but to the effect of the vascular disease itself in the different organs of the body. The heart hypertrophy and the high blood-pressure are nature's methods of meeting the consequences of the vascular disease. In consequence of the changes in the blood-vessels, one fragment after another of the kidney may be destroyed and replaced by connective tissue; but between these spots the kidney is largely normal. Wherefore, the urinary findings are those of a normal (or allegedly increased) water output containing some casts and albumin, the amount of the latter being an index to the amount of kidney involved through the sclerotic process. In the late stages of this so-called "*chronic interstitial nephritis*" the normal or "*increased*" water output gives way to a decreased one, and then the content of albumin and casts rises. Such a change means that more kidney tissue is being involved in the nephritic process.*

*It must be interjected here that "*chronic interstitial nephritis*" with high blood-pressure, etc., scarcely ever die primarily of their kidney disease. One third die of causes not at all associated with their vascular disease; one-third die by the cardiac route (which explains the increased albuminuria in the terminal stages of the disease); while the remaining third die of vascular disease of the brain, either hemorrhage or edema, the latter being falsely diagnosed "*uremia*" (see below).

While infections of the kidney are not ordinarily classed with the true nephritides, they might as well be. The kidneys here show the same changes and die in the same way as when a poison affects a whole or any part of the kidney. An infection involving the whole kidney (general intoxication) shows much albumin, many casts and a small water output. When the infected spots are small, as in the early stages of renal tuberculosis, these findings are all less intense. And since blood-vessel disease does not ordinarily go with the common infections, high blood-pressure and cardiac hypertrophy are usually absent in these cases of kidney infection. The best index to the probably infectious nature of a kidney lesion is the finding of leukocytes in the urine.

Erroneous Deductions to Be Guarded Against in Urinary Analyses in Nephritis.—The most serious mistakes, both in prognosis and treatment, which the physician is liable to make are dependent upon his attempt to judge from urinary findings (like the intensity or persistence of an albuminuria), whether his patient is going to develop an increased blood-pressure, "uremia," or some other alleged consequence of kidney disease. *Urinalysis gives us an index to what is going on in the kidneys and nothing more.* The possibilities of complications cannot be judged from the urine, *but must be discovered by other clinical methods.* This will be clear if it is remembered that none of those things which clinically are held to be consequences of kidney disease are really anything of the sort. These alleged consequences may occur simultaneously with kidney disease or entirely independently of such. Patients with complete loss of kidney function may show no "uremia" whatsoever, and others may die of what clinically is alleged to be a "uremia" without any kidney disease whatsoever. A few remarks will serve to show why this is so.

It is generally urged that the generalized edema, the "uremia," etc., of a patient, is secondary to the kidney disease. This is, in the main, incorrect; for double nephrectomized animals, or human beings who have had an only kidney removed, develop either no edema at all or only a very slight one, as compared with the edema developed, for instance, after the injection of some poison like uranium nitrate. Neither do they die with signs or symptoms which clinically we call "uremic," even though they live many days. But when we give an animal a "kidney poison" of some sort, such as uranium, it develops an edema in the course of a few hours, which at the end of about two days may have increased to represent 50 per cent. of the original body-weight of the animal. This means only one thing—*what we call the consequences of kidney disease are not consequences, but are the same thing as the kidney disease manifested in the different organs of the body*, and all due to the same poison which originally produced the kidney change. The headache, stupor, coma and convulsions of "uremia" are due, in the main, to an edema of the brain, the changes in sight to an edema of the optic nerve or retina, the vomiting to an edema of the medulla, and the generalized edema to a swelling of the body tissues generally, all induced through the same poison circulating through the body and

responsible for the edema of the kidney (nephritis). Conversely, the appearance of such clinical signs and symptoms should be attributed to an edema of the involved organs and not to the consequences of kidney disease.

What relation does the "uremia" of chronic kidney disease associated with cardiac hypertrophy, high blood-pressure, etc., bear to the uremia just discussed? Is it due to retained poisons which the kidney has failed to excrete? This "uremia," too, is also an edema of the brain, but it is induced this time through the defective blood supply to the brain brought about through vascular disease. These "uremic" attacks are periodic edemas, and are analogous to the periodic glaucomatous attacks (edema of the eyeball) to which these same patients are liable.*

MICROSCOPICAL EXAMINATION OF THE URINE

Introduction.—For microscopical examination of the urine it is again advisable to have as fresh a specimen as possible. On standing, due to change in temperature, to absorption of gases from the air and more particularly to bacterial decomposition, various changes may occur which will make the microscopist lose sight of the only important elements which he may need for proper diagnosis.

An apparently clear urine may contain considerable numbers of casts, or leukocytes, or of plasmolyzed (hemolyzed) red blood-corpuscles. On the other hand, intensely turbid, almost viscid urine may not contain

* These facts will serve to emphasize why, in treating patients with "chronic interstitial nephritis" or "chronic Bright's disease" with high blood-pressure, the primary diagnosis should read, vascular disease, and the purpose of our treatment should be its relief. We must stop treating the kidneys as something primary, and the high blood-pressure, cardiac hypertrophy, etc., as things bad in themselves, which they are not. We must do everything in our power to stop the progress of the blood-vessel disease itself which naturally raises the question of its origin. Everything has been named as a cause of blood-vessel disease, though that any of the things are really concerned can hardly be said to have been proved. However bad alcohol, gastro-intestinal poisons, etc., may be for an established vascular disease, this is not synonymous with saying that they cause it. Whenever a general intoxication strikes an organ, that organ is usually affected fairly uniformly, and so we should expect that, if any general poison were responsible for vascular disease, all parts of a blood-vessel, say all the media or all the intima, would be uniformly involved; but it is characteristic of vascular disease that it appears in spots. There must, therefore, exist for it a spotty cause, and not such a general cause as a generalized intoxication.

It is characteristic of microorganisms producing thrombotic changes in the smaller blood-vessels to give rise to just such spotty destructive lesions. In any case of vascular disease careful search should, therefore, be made for all possible infections. Of first importance, no doubt, stands syphilis. In cases where such a cause can be shut out with a fair degree of certainty, it is well to look for infected tonsils, infected teeth, infected ears, infected pelvic organs and old genito-urinary infections as sources of microbial infection of the blood stream with thrombotic changes in the smaller capillaries of the parenchymatous organs and in the vasa-vasorum of the larger blood-vessels; together with a scheme of these chronic foci of infection from accessible regions, together with a scheme of living directed toward a building up of the natural resistance of the body to infection, it has seemed to the writer that the usually progressive nature of "cardiovascular-renal disease" has been stayed, to which has often been added a decided recession in intensity of clinical signs and symptoms.

a single element of medical importance. It may be simply highly concentrated urine in which various urates or phosphates have been precipitated.

In the case of the apparently clear urines, the writer makes it a point to recall the *reaction* of the urine and then proceed at once to microscopical examination. In the case of the turbid specimens, it is well to make the following tests before this is done.

If there is much urine and turbid, simply *warm* [do not heat over 40° C. (104° F.) or boil] the urine. Urates which have fallen out (and the appearance of which is of no diagnostic importance) go back into solution. If the urine does not clear, add a little acetic acid. Phosphates which were formerly precipitated, now go into solution. A turbidity undiminished under these circumstances may be due to the presence of pus-cells, showers of kidneys cells, or considerable numbers of red blood-corpuscles. Verify or eliminate their presence by microscopical examination of the warmed specimen, or a fresh specimen of urine.

If the urine is not only turbid, but small in amount, remember that any of the ordinarily dissolved substances contained in urine may fall out in such concentrated and cooling urine. Verify the fact by adding to the urine an equal volume of distilled or ordinary tap water and warm (but do not overheat) this mixture.

Generally speaking, all these soluble turbidities are difficultly soluble salts (either phosphates or carbonates if the urine is alkaline, or urates and uric acid if the urine is acid) and of little or no clinical significance. If such crystalline turbidities fall out in the urinary passages they may give rise to stones, to "sand" attacks, or the irritations incident to "phosphaturia." *But the diagnoses of these conditions cannot be made from urinary examinations alone.* Any number of entirely normal individuals who sweat much or drink little water (have concentrated urines) or who eat much protein (produce much phosphoric acid and urates) may show these findings. Precipitated phosphates will appear regularly in the alkaline urines of pure vegetarians, in meat eaters, either well or ill, who are receiving alkalis in sufficient quantity by mouth, rectum, or intravenously to void neutral or slightly alkaline urine, and in all victims of genito-urinary disease in whom ammoniacal decomposition of the urine is responsible for a neutralization of the acid urine as this comes from the kidney. In the last-named illustration other urinary findings besides the existence of a phosphate or carbonate precipitate make the diagnosis.

The Technic for Microscopy in Urinalysis.—In spite of the usual advice to the contrary, the writer thinks it best to examine *non-centrifugalized* specimens of urine first. Introduce a clean volumetric pipet with the top closed by a finger to the bottom of the (preferably conical) vessel in which the urine has stood while other examinations have been made, and by releasing the pressure of the finger a little allow a few drops of the thicker urine to ascend the pipet. Again close the opening of the pipet and transfer a drop or two of the urine to a clean slide.

The author usually makes a first examination using no cover glass. If a cover glass is used, it should be large enough, or the drop of urine small enough so that much liquid is not forced out at the edges of the glass. This makes the lighter elements (like cells and casts) "float off" and so they may be missed.

A proper microscopic urinary examination cannot be made with much light. Stop down the lower diaphragm of the ordinary microscope to a point where very little light enters.

It is safe in ordinary practice to eliminate as of no clinical importance all the crystalline bodies found (phosphates, urates, carbonates, uric acid, etc.), as well as the amorphous elements which have this chemical composition. The important elements to look for are: (1) casts, (2) leukocytes, (3) red blood-corpuscles, and (4) isolated cells. To this list should be added (5) cylindroids and (6) bacteria of various kinds. But excepting as certain morphological findings in the commoner infections (gonorrhea, tuberculosis, streptococcus or staphylococcus infections) may suffice to make a provisional diagnosis, it should be remembered that the last named field is a rather slippery one and is therefore best left to the expert in bacteriological technic.

1. CASTS.—Casts are of importance as an index to dissolution phenomena in the kidney. They serve to locate disease in this organ. The substances which give rise to nephritis (like acids of various kinds) make the proteins of the kidney "go into solution." The proteins which bind the kidney cells to their supporting tissues are, however, more soluble than most of those in the parenchymatous cells themselves. The parenchymatous cells tend, therefore, to loosen in mass from the supporting tissues in the kidney, and so are swept as casts into the urinary stream. Thus are formed "epithelial" cells.

With more prolonged action of the acid (and like substances) the cellular structure is lost and "granular" casts are formed. With still greater and more prolonged action of the acid, these granular casts become "hyaline." Differentiation between these different casts is not of diagnostic or prognostic importance. They all mean destruction of the kidney and nothing more.

The numbers of casts are, however, an index to the amount of such destruction which is going on in the kidney. Many casts mean much, and few but little destruction. The former need not, however, be synonymous with serious kidney disease and the latter with mild. This all depends upon the causes which lie behind the abnormal production and accumulation of acids (and similarly acting bodies) present in the kidney. A hard athletic endeavor may be responsible for the first and of as little significance to the individual; while in the second we may be dealing with the beginnings of a vascular disease involving the kidney (chronic Bright's disease). Obviously, a doctor and not a microscopist is needed to make proper appraisement.

2. LEUKOCYTES.—Leukocytes are of importance because they indicate infection. In all the acuter types of genito-urinary infection (from kidney to urethral opening) the polymorphonuclear types of leukocytes

predominate. In the more chronic ones (like syphilis and tuberculosis) the large and small mononuclears may become prominent. The largest numbers of leucocytes occur, of course, where the infected areas are extensive, as in bladder infections or large infections of the kidney or kidney pelves. Physical examination must give the final answer as to exact position or positions.

Greater difficulties are experienced in determining where smaller numbers of leukocytes appearing in the urine may come from. In the absence of casts the lesions are, naturally, to be placed below the kidney.

Where, on the other hand, infection of the lower urinary passages can be excluded, the association of leukocytes with casts is always to be regarded as strongly indicative of infection of the kidney (infectious nephritis). If there are no increases in blood-pressure, and especially if an occasional slight temperature (99° F.) can be discovered, added weight is given to this diagnosis. The matter is of tremendous importance because many of the "chronic nephritides" and "chronic Bright's disease" cases without high blood-pressure are of this group, and since the infection is commonly metastatic (is, in other words, derived from some distant point of infection, like a tonsil, tooth or toe-nail) much can often be done by proper surgical attention to the readily accessible and too often neglected point of original infection.

The purely toxic types of nephritis (as those following poisoning with the metals, or in the wake of the toxins produced in eclampsia, etc.) are not apt in the first stages of the disease to yield any or more than a few leukocytes. Later (as kidney substance is destroyed) this number may increase as in other types of "sterile inflammation," but a little careful consideration of the whole patient will do much to give proper emphasis to the real meaning of the urinary findings.

3. RED BLOOD-CORPUSCLES.—The finding of red blood-corpuscles in the urine means that hemorrhage through rupture of a blood-vessel or by diapedesis is occurring somewhere in the genito-urinary tract. Often, the presence of casts, leukocytes and physical findings will show where the lesion is located as well as its true significance. It should be remembered that bleeding, unassociated with other microscopic findings, may occur in benign and malignant tumors of the genito-urinary tract.

Considerable blood in the urine will usually give color to the urine, but when there is only slight bleeding, the finding of red blood-corpuscles is necessary to discover the fact. This is easy if the red blood-corpuscles retain their biconcave disc-like shape, and retain their yellow color. But because the concentration of the urine is rarely that which is just necessary to bring about this happy result, the red blood-corpuscles are more commonly found either plasmolyzed (as swollen, pale, non-nucleated "shadows" of their former selves), if the salt concentration of the urine is low or its acid content high; or shrunken (crenated), if the concentration of the urine is above that of ordinary blood-plasma.

4. ISOLATED CELLS.—The practitioner can become familiar with the appearance and, therefore, with the point of origin of the isolated cells which he may find in urine only as he will study first their normal his-

tology. To know them is of service at times in recognizing the position of a genito-urinary lesion. The problem, is however, complicated by the fact that the isolated cells from the different portions of the genito-urinary tract lose their nuclei and swell and shrink with variations in the concentration and acidity of the urine. Contamination with vaginal epithelium (as well as vaginal mucus or pus) may be avoided in women by having them take a douche with physiological salt solution before voiding the sample to be examined and by having them separate the labia, and voiding into two vessels, the first portion being considered as contaminated by any materials (like pus) in the urethra, the latter as the purer urine from the bladder and upper urinary tract. The similar trick of having men void into two or three separate glasses works, of course, to the same end.

5. CYLINDROIDS.—Cylindroids appear, for the most part, as hyaline threads. They are of the shape of hyaline casts, except that they may be longer and, often, thread-like at one end instead of rounded. When amorphous or crystalline particles stick to them these cylindroids may look not unlike granular casts. Confusion arises, naturally, from mistaking these cylindroids for casts. They probably are of no significance so far as being indicative of kidney disease is concerned. They are often called "mucus" casts. The substance of which they are composed is undoubtedly "mucoid" in character, but chemically it does not give the orthodox reactions for mucus. They are common in highly concentrated urines such as are found in the heavier intestinal intoxications and the acuter infections. They disappear when more water comes through the kidney and are significant only, so far as the author knows, of what S. P. Kramer has well, if inelegantly, termed a "snotty" kidney.

SUMMARY

With the remarks outlined above in mind, we may now make the following summary in rather dogmatic terms of what are the indispensable urinalytic tests, and those of greatest interest to the general practitioner, indicating at the same time how these may be so arranged that in ten minutes or less a really safe estimate may be made of their significance for the patient; and how in a few seconds of work subsequently an accurate picture may be maintained of how a patient is faring in the course of his disease or in consequence of therapeutic endeavor.

1. Learn from the patient's history, from the report of the nurse or through direct personal measurement, the quantity of urine being put out by the patient in each twenty-four hours. If the amount runs above 1,000 c.c. (34 ounces) daily, it may be assumed that sufficient kidney function is left to be considered adequate, provided this can be maintained. Any amount of urine above this daily liter is to be considered in the patient's favor so far as his kidney function is concerned.

Amounts below this must not, however, at once be considered evidence of defective kidney function. They may be the result of nothing more than excessive sweating, great catharsis or lack of fluid intake. Give the patient, in consequence, a half liter of water and repeat this two hours later. If the urinary secretion is definitely increased (by 400 to 500 c.c. [13.5 to 17 ounces] in the first, or certainly in the second two-hour period), the prognosis is, on the whole, favorable. But if no such increased diuresis results, careful investigation of the multitude of causes lying outside of the kidney, or in the kidney itself, must be made, and a proper value set upon each of them. Look for a high constitutional acid intoxication of any sort, or, more specifically, for respiratory or heart disease, anemia, or an interference with the oxygen-carrying power of the blood, arteriosclerosis, pressure upon the vessels of the kidney, intoxications of the kidney itself and direct infections of this organ.

2. Use the color, odor and turbidity of the urine as quick hints in the direction of the presence of abnormal coloring substances, the presence of volatile aromatic compounds (like acetone) and the presence of abnormal materials like pus or blood. If a specific gravity test is made, use it for what it is worth and nothing more. Even small amounts of urine may show a low specific gravity if the patient is inadequately fed, and mean nothing regarding kidney function; and on a normal diet any person who drinks water freely will void a large amount of low specific gravity. Remember that even a diabetic may void large amounts of low specific gravity. Turn, therefore, to sugar tests, to discover if such is present and get an answer in reliable fashion.

3. Test the acidity of the urine with two drops of methyl red solution, or dip a strip of methyl red paper into it. Consider all urines which show an acid reaction to this indicator as on the dangerous side of the ledger, and feed such patients alkali until their voidings remain persistently alkaline to this indicator. It must be remembered that a urine which is acid when secreted by the kidney, may be alkalized in the bladder through bacterial decomposition of the urea into ammonia. Use other clinical methods to discover such a fact. It must be remembered also that in kidney disease which involves only portions of the kidney (as in the earlier stages of chronic interstitial nephritis associated with vascular disease, in the metastatic infections of portions only of the kidney, etc.) a urine neutral or even alkaline to methyl red may be discovered. There may exist also an abnormal production or accumulation of acid in some one organ of the body (as in edema of the brain, in "uremia" or in glaucoma), or in pieces of the kidney only, without the general acid intoxication being high enough to yield a urine acid to methyl red. In such instances general clinical observations must lead to a giving of alkali (and of various dehydrating salts like magnesium sulphate) in order to maintain the constitutional alkalinity.

4. It is well in all instances, but it is imperative in those in which acidity determinations have shown that the patient is inclined, tempo

rarely or persistently, to an acid intoxication, to make a ferric chlorid test for diacetic acid. A positive reaction is to be interpreted as indicative of carbohydrate starvation. By another test it may be discovered if the patient is a diabetic. Whether he be a diabetic or not—and the more important group is that of the *non-diabetics*—see to it at once that carbohydrates are fed by mouth, by rectum or intravenously as the urgency of the situation may demand. At the same time eliminate the fats from the diet. Keep up this treatment until the ferric chlorid reaction disappears. Where the powers for utilizing carbohydrate are too heavily depressed by causes which lie beyond our control (as in the severer diabetics), the ferric chlorid reaction will, of course, persist, but we may have the satisfaction, except in the severest diabetics, of seeing its intensity diminish.

5. Perform a Fehling's test on the urine. If the test is negative proceed to the analysis for proteins. If positive, make sure that the urine has not had formaldehyd added to it, or that the patient has not been receiving a formaldehyd derivative (hexamethylenamin; urotropin) or chloral. If the patient is a woman, make sure that the reduction is not due to milk-sugar, either because she is pregnant or lactating.

6. Perform a cold nitric acid test on the clear urine. If, with due care, a positive reaction is obtained, determine by other methods the source or sources of the albumin. The intensity of the reaction may be taken as a rough index to the amount of albumin present in the urine. If a more accurate figure is desired, do an Esbach quantitative test with Tsuchiya's reagent.

It must be kept in mind that albumin becomes "dissolved" in the urine not only because of the solution of the genito-urinary organs in the urine, but because of the solution of red and white blood corpuscles after these have been shed into the urine from the diseased genito-urinary apparatus. See how large a part is played by the latter element by examining the urine microscopically.

If a lesion of the genito-urinary apparatus below the pelvis of the kidney can be excluded, use the intensity of the albumin reaction as an index to the amount of kidney substance involved (*use the ability of the kidney to put out water as an index to the amount of kidney substance NOT involved*). Check the opinion regarding amount of kidney involvement by searching for casts and determining whether these are present in large or small numbers. Draw no unwarranted conclusions from examination of the urine regarding "uremia," high blood-pressure, generalized edema or other alleged consequences of kidney disease.

7. Prepare to examine the urine microscopically, but before doing so recall whether you are dealing with concentrated or dilute urine. All concentrated, cooling urines are likely to throw down a heavy precipitate. If such a precipitate is present, check its character by diluting the urine, by warming it gently and by adding a little acid. Precipitates due to

the unimportant phosphates, carbonates and urates clear under these circumstances.

Put a drop of the sediment from the urine under the microscope and examine especially for (1) casts, (2) leukocytes, (3) red blood-corpuscles, (4) isolated cells from the different portions of the genito-urinary apparatus, (5) cylindroids, (6) bacteria.

If the urine is alkaline, *casts* may be so completely dissolved as to disappear. This fact must be remembered in order that a kidney lesion may not be thus overlooked. If the urine is neutral or acid in reaction, the finding of casts not only confirms the diagnosis of a kidney lesion, but their number may be taken as an index to how much of kidney substance is in a state of pathological change. Draw no unwarranted conclusions regarding specific types of kidney disease because of variations in the type of casts.

Use the presence of polymorphonuclear or mononuclear *leukocytes* as an index of infection somewhere in the genito-urinary apparatus. Determine its position by other methods of examination. If the origin of the leukocytes can be traced to the kidney itself, incline to the diagnosis of infectious nephritis, considering not only the possibilities of tuberculosis and syphilis, but the far commoner chronic infections due to streptococci and staphylococci. Since nearly all these infections are blood-borne and metastatic, look for entrance points of infection in tonsils, teeth, antra, etc.

Red blood-corpuscles only mean a destructive lesion somewhere in the genito-urinary tract with hemorrhage by rhexis or diapedesis. If the bleeding is unassociated with casts, leukocytes and similar materials, think of the possibilities of a bleeding polyp or a bleeding benign or malignant tumor somewhere in the genito-urinary apparatus.

The finding of *isolated cells* which are characteristic morphologically of the different portions of the genito-urinary tract may help to locate a lesion, but to do this properly the examining physician must be familiar with the normal histology of the genito-urinary apparatus and with the changes which its different cellular structures may suffer on exposure to urines of varying concentration and acidity.

Cylindroids (mucus casts or pseudocasts) should not be confused with true casts. Cylindroids are indicative of what may be termed a dirty kidney, but they are not of pathological significance in the ordinary sense of the word.

Finally, an attempt may be made to identify by simple staining methods some of the commoner infectious organisms which appear in urine. The possibilities for grave errors in diagnosis and based either upon positive or negative findings must, however, not be forgotten.

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CHAPTER XI

THE CEREBROSPINAL FLUID AND ITS RELATION TO HEALTH AND DISEASE

BY DAVID J. KAISER, M.D.

HISTORICAL SURVEY

Historical survey, p. 475—Physiology of the cerebrospinal fluid, p. 476—Physical and chemical characteristics of the cerebrospinal fluid, p. 486—Technic of lumbar puncture, p. 495—Technic of cisternal puncture, p. 510—Methods of examination of the cerebrospinal fluid, p. 511—Cerebrospinal fluid in syphilis of the nervous system, p. 527—Relation of secretion and absorption of the cerebrospinal fluid to intraspinal therapy, p. 531—Lumbar and cisternal puncture as therapeutic procedures, p. 534—The meninges, description and differentiation, p. 536—The cerebrospinal fluid in neurology and psychiatry, p. 541.

A historical survey of the literature of the cerebrospinal fluid reaches into the dim era of the past, hundreds of years before the birth of Christ. Herophilus (300 B. C.), a dissector of human bodies, knew of the presence of the cerebral ventricles, where he placed the seat of the soul, and of the choroid plexuses, but knew nothing of their function, nor did he describe the presence of fluid in the ventricles, although it would seem that the presence of fluid in them could hardly have escaped his attention. Erasistratus (330–250 B. C.) and Galen described the ventricles of the brain and their connection with one another, but made no mention of the cerebrospinal fluid. If they were cognizant of the presence of fluid in the ventricles, which is doubtful, the connection between the cerebrospinal and ventricular fluid surely was unsuspected. Indeed, although hydrocephalus was known to the ancients, the presence of cerebrospinal fluid in living individuals was never referred to. After a lapse of centuries, the anatomist Vesalius (1543) makes no special reference to the spinal fluid. Varolius (1543–1575) described the ventricular fluid. He thought the choroid plexuses acted as pumps to pour water into the ventricles, and also referred to the spinal fluid. Credit for the description of the cerebrospinal fluid is given to Contugno (1784), who also described the presence of the cerebrospinal fluid in turtles and fishes. Robert Whist, in 1764, described tuberculous meningitis, and four years later wrote a book on the diseases of the brain under the title, "Observations on the Dropsy of the Brain." Albertus von Haller (1708–1777) described the cerebrospinal fluid in his book, "First Lines of Physiology," although he probably did not know the correct relationship between this fluid and that in the ventricles of the brain. Coligno, who spoke of the cerebrospinal fluid in 1764, thought it was present only after death. In fact, not until 1840 was the connection between the fluid in the ventricles of the brain and that in the subarachnoid space pointed out by Magendie,¹ who described the point of exit of the fluid from the ventricles into the subarachnoid space. He accurately described the appearance of the cerebrospinal fluid and spoke of its function as a mechanical protector or water-bed for the brain and cord.

* The methods of clinical research were enriched in a more recent era by the attempt of Middeldorff² to obtain the fluid from the ventricles

for examination by puncture, which was done through a trephine opening in the skull. The first withdrawal of the spinal fluid was effected by an American physician, L. Corning,³ who in 1885 inserted a needle between the spinous processes of the last two dorsal vertebrae, for the purpose of injecting an anesthetizing solution into the spinal canal. W. Essex Wynter,⁴ in 1889, described drainage of the spinal canal in the treatment of cases of tuberculous meningitis, introducing a cannula armed with a trochar into the spinal canal at the level of the second lumbar spine, until the fluid rushed through the cannula. A small rubber tube was then inserted through the cannula into the canal, affording continuous drainage.

The simplification and perfection of the procedure of lumbar puncture, not only for therapeutic purposes but also so that the cerebrospinal fluid could be safely and easily obtained for clinical study, are due to the epoch-making work of Quinke,⁵ whose first publication appeared in 1891, following a description of his method of lumbar puncture and the publication of the results of two cases of chronic hydrocephalus treated by withdrawal of the spinal fluid. The technic, as outlined by Quinke, has not been changed fundamentally to this day, and the ease and comparative safety with which fluid can be withdrawn from the living human being have enabled Quinke and a host of followers to add a wealth of data to our stock of knowledge concerning the relationship of the cerebrospinal fluid to health and disease.

It is the writer's purpose in the following pages to give a résumé of the more important anatomical and physiological facts necessary for an understanding of the mechanism of the secretion and absorption of the cerebrospinal fluid, to outline the rôle played by the fluid in the protection and nutrition of the central nervous system, to point out the methods for obtaining and examining the fluid and to discuss the value of these examinations in diagnosis, prognosis and treatment of diseases of the central nervous system.

PHYSIOLOGY OF THE CEREBROSPINAL FLUID

Mechanism of Secretion.—Like most of the problems concerned in a consideration of the cerebrospinal fluid, that of the origin of the fluid has not been settled with absolute certainty. Physiologists to-day believe that the fluid is secreted from the blood, principally by the *selective action* of the cells of the choroid plexus of the cerebral ventricles, and that it is a true secretion rather than a transudation from the blood vessels. The cerebrospinal fluid is entirely unlike any of the other fluids of the body, with the exception of the aqueous humor of the eye with which there is almost complete anatomical and physiological correspondence (Wegeforth and Weed⁶). This is the original view of Faivre,⁷ and has been accepted by such physiologists as Dixon and Halliburton,⁸ Frazier and Peet,⁹ Pettit and Girard,¹⁰ Mott¹¹ and others. The fluid secreted by the choroid plexuses is poured into the cerebral ventricles and passes through the foramina of Munro into the third ventricle and through the aqueduct of Sylvius into the fourth ventricle, escaping into the subarachnoid space through the foramen of Magendie and the foramina of Luschka. From here the fluid passes over the hemispheres, dipping down into the spaces between the sulci and around the basilar structures in the cisternæ between the pia and arachnoid

and downward into the subarachnoid space surrounding the spinal cord. In view of the similarity of the selective action of the cubicle cells of the choroid plexus to that of the cells of the lacrimal gland in the secretion of the tears, Mott¹¹ has aptly termed the secreting apparatus concerned in the elaboration of the cerebrospinal fluid, the choroid gland, a term that Halliburton¹² has also adopted. Whether the cerebrospinal fluid is a true secretion or a dialysate from the blood has recently been studied again by Forbes, Fremont-Smith and Wolff,¹³ who have attempted to study the question anew by introducing pigment granules into the subarachnoid space and then injecting hypertonic salt solution into the circulation. Under such conditions the pigment was soon found within the vessels of the choroid plexus. This indicates, as the investigators point out, that the direction of flow of cerebrospinal fluid through the choroid plexus may be reversed by increasing the osmotic pressure of the blood. Supposing the choroid plexus to be purely a secreting gland, the mechanism of such a reversal of flow would be difficult to understand. They therefore aver that their observations add to the accumulating evidence that the choroid plexus may be regarded as a semi-permeable membrane and the cerebrospinal fluid as a true dialysate.

But there is still a considerable amount of evidence pointing to another source for the cerebrospinal fluid, and though the choroid plexus no doubt has by far the greatest significance in the secretory mechanism, a part at least—if only a very minor part—is played by the perivascular system of the central nervous system, bringing to the fluid the excretory substances of brain metabolism chiefly, and possibly also the secretions of the pituitary gland. This view is shared by such investigators as Weed,¹³ Plaut, Rhem and Schottmueller¹⁴ and others. The case of Dandy and Blackfan,¹⁵ of acute hydrocephalus with complete obstruction of the ventricles in which five c.c. of spinal fluid were obtained by lumbar puncture and were quickly replaced after withdrawal, is more or less confirmatory of this view; and yet if—as Weed¹³ states—the cerebrospinal fluid is partly formed, like the lymph of the body in the perivascular spaces, by exudation from the blood vessels, it is difficult to understand—as Halliburton¹² argues—why readily diffusible substances do not enter the cerebrospinal fluid more easily in the normal state.

Permeability of Choroid Plexus.—To many substances (chemicals, bacteria, toxins, antibodies) the choroid plexus acts as a barrier, especially under normal conditions. Even protective antibodies and other immune bodies fare no better under such conditions, and only when the choroid plexus is irritated by intraspinal injection of foreign or other sera or by lumbar puncture or during the course of a systemic disease with, presumably, an alteration in the histological structure and activity of the gland, do these bodies appear in the fluid. Flexner and Amoss¹⁶ have recently shown that this occurs in poliomyelitis. They proved experimentally that in passively immunized monkeys neutralizing antibodies for the poliomyelitis virus can be made to pass from the blood into the cerebrospinal fluid by increasing the permeability of the choroid plexus by an aseptic inflammation of the latter induced by intraspinal injections of normal horse serum. These experiments shed a light on the probable value of serum therapy. It has been pointed out that the choroid plexus in its normal state may act as a barrier to the passage of protective or immune bodies, but in the course of poliomyelitis

the meninges and the choroidal secreting complex are inflamed and injured, thus becoming readily permeable to the "protein of the plasma and to the immune bodies contained in it." And when these appear in the blood, as immunity becomes established, they permeate the central nervous system through the intermediation of the cerebrospinal system with a neutralization of the virus of the disease. It is reasonable to suppose that this mechanism serves also to explain the rationale of intraspinal medication in other diseases of the central nervous system.*

The writer and Strauss,¹⁷ also Barbat,¹⁸ have advanced a somewhat similar explanation for the presence of arsenic in the spinal fluid of syphilitic patients after intravenous injections of salvarsan and after combined intravenous and intraspinal injections or after simple withdrawal of spinal fluid.

Kolmer and Sekiguchi¹⁹ have shown that after the transfusion of syphilitic serum into normal dogs the syphilitic "reagin" appeared in the spinal fluid in small amounts within three hours and disappeared within forty-eight hours. The same applied after transfusion of dog typhoid immune serum into dogs. In all probability this is also true of the syphilitic "reagin" in the cerebrospinal fluid in human syphilis, although here there is the added factor, in many instances, of a coincidental pathological involvement of the tissues of the central nervous system, with probably an alteration of the secreting mechanism also, permitting remedies injected intravenously to reach the cerebrospinal fluid.

Indeed, the doctrine of the complete impermeability of the choroid plexus must soon give way under an increasing accumulation of evidence tending to show that under conditions existing in disease certain drugs and immune substances, as well as bacteria and their toxins, pass the barrier of the choroid plexus and make their way into the cerebrospinal fluid.

Absorption of the Cerebrospinal Fluid; Factors Influencing Secretion; Pressure of the Cerebrospinal Fluid.—It is essential to consider the factors influencing the rate and amount of secretion and absorption of the cerebrospinal fluid, in view of their importance in many of the problems concerned in disease of the central nervous system and in the surgery of the brain and spinal cord. As will be shown, many of the symptoms arising in patients with tumors of the brain and infections of the cerebrospinal system are due in great measure to disturbances in these factors of secretion and absorption. For example, the chief symptoms in tumor of the brain—headache, choked disk and vomiting—are due to the production of a secondary hydrocephalus and can be relieved by surgical procedures such as lumbar puncture, decompression and callosal puncture, designed to reduce the pressure of the cerebrospinal fluid to normal. Normally the choroid gland is constantly elaborating the cerebrospinal fluid, and there is reason to believe that the fluid secreted is very rapidly absorbed, but here again our knowledge of the mechanism is not absolute. The amount of cerebrospinal fluid in the normal human individual varies considerably. The figures given by various authorities vary from 60 to 150 c.c.

* This hypothesis is based on the assumption that the cerebrospinal fluid plays a part in the conveying of metabolic substances to the nervous tissue. However, it must be remembered that this view is not universally accepted.

Cotugno	120-150 c.c.
Magendie	62 "
Testut	100-150 "
Luschka	75 "
R. Wagner	82 "

The ventricles normally contain about 30 c.c. of fluid.

The diffusion process is most rapid in the subcerebellar region and slowest in the lower spinal region. Substances injected into the subarachnoid space take from twenty minutes to two hours to be generally distributed. The direction of circulation of the cerebrospinal fluid seems to be from the ventricles, where secretion occurs, downward. However, an active circulation of the cerebrospinal fluid has not been proved nor has the circulation of the fluid from the spinal subarachnoid space upward toward the ventricles been demonstrated, though a certain amount of diffusion in this direction may occur, influenced by such factors as position, pressure, respiratory efforts, emotions, etc. The work of Kramer²⁰ is suggestive, regarding an ascending current in the central canal of the spinal cord, but has not as yet been confirmed.

Experimentally certain substances injected into the subarachnoid space, especially in the cranial portion, are almost immediately absorbed into the venous channels. Normal salt solution is taken up in very large quantity and readily diffusible drugs like adrenaline or atropine act at least as quickly as if injected directly into the blood. Dandy and Blackfan¹⁸ have shown that neutral phenolsulphonephthalein—a readily diffusible dye—when injected intraventricularly, reaches the blood of the torcular herophili within a few minutes and the urine in five to ten minutes, and the total amount injected can be recovered from the bladder within two hours. If the ventricles are blocked, preventing the free access of fluid into the subarachnoid space, as in certain types of hydrocephalus, as pointed out by Frazier and Peet,⁹ practically no absorption of the dyestuff occurs, even after two hours. On the other hand, nondiffusible substances, such as peptones, are very slowly absorbed, as Halliburton²⁸ has shown. This difference in the rate of absorption of various substances from the subarachnoid space practically disposes of the theory of a valve-like opening into the blood channel as an exit for the cerebrospinal fluid—a view long held by most physiologists.

Absorption occurs, as Weed¹³ has proven, chiefly by a process of filtration through mesodermal cell membranes of the arachnoid villi into the venous sinuses in the skull. According to Dandy and Blackfan,¹⁸ the mechanism of absorption is a diffuse one on the part of the capillaries of the entire subarachnoid space, but in opposition to this view is the argument of Weed, that the arachnoid is nonvascular and that the pia is also wholly lacking in a capillary bed. Hassin^{13a} and others believe that the choroidal cells have an absorptive function and may serve to remove harmful products of metabolism of the nervous

s.

The cerebrospinal fluid is absorbed much more readily and in greater amount by the cranial than the spinal subarachnoid; most rapidly in the subcerebellar region, and slowest in the lower spinal region, the

latter taking an insignificant part in the total amount of absorption. Under abnormal conditions the rate and amount of secretion of cerebrospinal fluid may be greatly altered, but so far as we know this departure from the normal—with but one exception—is always in the direction of an increase. There is probably an accessory pathway for absorption of fluid into the lymphatic system, but this plays an insignificant part except from the isolated spinal subarachnoid space. Hill²¹ has shown that methylene blue injected into the cerebrospinal fluid passes directly into the venous sinuses and in 10–20 minutes is secreted in the gastric juice and the urine. The lymphatics of the neck are not colored within this period of time and even after an hour are only slightly tinged with color. There is thus an intimate connection between the cerebrospinal fluid and the venous system, rather than with the lymphatic system.

According to Frazier,²² in brain tumor and other space-constricting conditions in the cranial cavity, like acute hydrocephalus, there is an increased rate of secretion and a decreased rate of absorption. Inasmuch as absorption is chiefly by way of the venous channels, tumors at the base causing pressure on the large venous sinuses are more apt to give secondary hydrocephalus and the concomitant symptoms of headache, vomiting and choked disk, than are cortical tumors. This would also apply in basilar meningitis with an exudate. The fluid re-accumulates very rapidly after tapping in these conditions, and in an instance cited by Frazier,²² 150 c.c. of fluid removed by puncture of the ventricle re-accumulated within 20 minutes, suggesting a disturbance of secretion possibly through the increased vascularity of the choroid plexus. But attempts to deprive the plexus of part of its blood supply by carotid ligation, in an effort to reduce the rate and amount of secretion in hydrocephalus, have been for the most part unsuccessful. In many cases of hydrocephalus there is free communication between the ventricles and the subarachnoid space, and in most instances lumbar puncture is as successful in freely emptying the ventricles as ventricular or callosal puncture, according to Cushing.²³ Experimental efforts thus far have shown but one drug which tends to reduce the amount of secretion of cerebrospinal fluid, viz., extract of thyroid gland. Frazier²⁴ has shown that extracts of thyroid gland have been successful experimentally in causing a primary but temporary fall of blood pressure, with a transitory increase in cerebrospinal fluid production, followed by a prolonged period of decrease of outflow through a specific inhibitory effect on the choroid gland. Clinically the results have been very encouraging in a small number of cases, though the time has been too short to permit a definite opinion concerning the value of the injection of this drug in such conditions as hydrocephalus. Experimentally the injection of extracts of brain and of choroid gland is known to cause an increase in the secretion of spinal fluid, as Halliburton²⁵ has shown. There is probably present in these extracts a hormone which stimulates the activity of the cells of the choroid gland, and which is the result of brain activity. It can be demonstrated in the cerebrospinal fluid of patients who are the subjects of extensive brain catabolism, as, for example, in general paresis. It resists boiling, does not pass through a Berkefeld filter and acts qualitatively like cholesterol, though to a greater degree. Other factors which tend to cause an increase are an excess of carbon dioxide or a lack of oxygen in the blood, and volatile anesthetics

which act by influencing respiration or by a direct stimulating action on the secreting gland.

Cappelletti²⁶ showed that ether and pilocarpine increased the flow and atropine diminished it. Dixon and Halliburton²⁷ confirmed these facts. Splenic extract, according to Frazier and Peet,²⁸ caused a marked drop in blood pressure and a rise in the flow of fluid of a temporary character, which was compensated for by a marked decrease in the rate or even a temporary cessation of the flow coincident with the gradual return of the blood pressure. Liver extract caused a marked decrease in the rate due to a sudden fall of arterial blood pressure affecting the cerebral sinuses, while brain extract caused marked increase in flow independent of blood pressure factors. They conclude that the sudden increase in the rate of flow following the use of organic extracts is due to sinus distention which forces out fluid already present in the ventricle and in the cisternæ.

The influence of blood pressure on secretion is important. The pressure of the cerebrospinal fluid is about the same as that of the venous sinuses. According to Howell,²⁷ any rise in intracranial pressure raises venous pressure by compression of the veins and an acceleration of the outflow of fluid from the subarachnoid space into the venous channels. An increase in venous pressure causes a rise in intracranial pressure, due to compression following the expansion of the venous walls and to a retardation of inflow of fluid into the venous channels. Thus compression of the veins of the neck causes a rise in the pressure in the cerebral veins and a coincidental rise in intracranial pressure. "The cranial cavity," as aptly pointed out by Weed and McKibben,¹³⁹ "is relatively fixed in volume and is completely filled by the brain, cerebrospinal fluid and blood; variations in any of these three elements may occur, compensation being afforded by alteration in the volume of one or both of the remaining elements." As long as the intracranial pressure remains lower than that of the vessels supplying the brain, the circulation through the brain is not markedly affected; but if it increases above the pressure in the arteries, the circulation through these vessels is slowed and finally stopped, cerebral anemia occurs, and unless compensated, coma results and finally death. As the circulation is slowed carbon dioxide accumulates in the blood, the medullary cardio-inhibitory center is stimulated, slowing the heart beat, while at the same time the vasomotor center in the medulla is also stimulated, causing a general vasoconstriction throughout the body, with a consequent rise in arterial pressure. Thus cranial circulation is reestablished (Cushing).²⁸

Frazier and Peet always found that an increase in the rate occurred coincident with a fall in blood pressure and vice versa. With a fall in blood pressure there is a sudden dilatation of the cerebral sinuses and a forcing out of fluid from the ventricles and the subarachnoid space, without an appreciable effect on the choroid plexus. High blood pressure is not accompanied by high cerebrospinal-fluid pressure unless there is a coincidental increase in venous pressure. The pressure of the cerebrospinal fluid is primarily due, aside from all circulatory factors enumerated, to the secretory activity of the cells of the choroid plexus. Normally this tension varies from 90-150 mm. of water or from about 6½-12 mm. of mercury. The following table from Mestrezat²⁹ will show the figures of numerous investigators:

482 CEREBROSPINAL FLUID IN HEALTH AND DISEASE

Cybierski	72- 90	mm. of water
Adamkiewicz	80-100	" " "
Key and Retzius	160-200	" " "
Bergmann	80-160	" " "
Quinke	40-130	" " "
Ayer	100-200	" " "
Falkenheim	160-200	" " "
Schulzen	52-100	" " "
Krönig	125-150	" " "
Parisot	100-150	" " "
Boveri	170-200	" " "

It should be borne in mind that, in evaluating pressure figures, it is necessary to take into consideration whether the pressure was taken in the lying or in the sitting position, the type of instrument employed, and whether a water or mercury manometer was used. On account of the great variation of these factors and the lack of uniformity in reading the results, the taking of pressure fell into more or less disuse by the profession. Even with a satisfactory apparatus the pressure can be made to vary considerably in the same individual by the position of the needle in the subarachnoid space, the degree of muscular contraction of the patient, the depth of respirations, emotional factors and pain. Extraneous factors must be taken into consideration. In hospital practice the readings of different individuals have varied in the same patient, so that in any given case it is wise, in taking pressure readings, to have the observations checked up or, preferably, made by the same observer. When the cerebrospinal fluid is under very marked tension, this fact can be determined by an observer experienced in the use of an ordinary Quinke needle, by the force with which the fluid issues from the needle. High pressure fluids spurt from the needle in a characteristic and unmistakable manner, but experience has shown—especially in surgical conditions of the skull—that the use of a manometer of one type or another is not only more accurate but more safe. Frazier²² uses the mercury manometer devised by Landon and regards pressures over 12 mm. of mercury as suspicious, while higher than 20 mm. is regarded as pathological. With the water manometer, pressures up to 200 mm. are not infrequently encountered. Pressures between 300 and 500 mm. are high and should be looked upon as pathological. A pressure of between 500 and 700 mm. of water is very high and infrequently encountered, while pressures up to 1,000 mm. are very rare. According to Quinke,⁶ the readings in children are about one-third less than in adults. According to Ayer, pressures between 200 and 250 mm. of water are suspiciously high; between 250 and 300 mm., definitely pathological. Pressures over 300 mm., according to him, are probably always due to intracranial lesions. These figures are determined with the patient lying on the side, with the spine horizontal and the head in alignment. In the sitting position the figures are about double those given for the recumbent position.

The pressure of the cerebrospinal fluid under normal conditions varies but little within certain specified limits. As far as known, there is usually an increase of pressure in intracranial disease—rarely a decrease. Congenital anomalies, the exact natures of which are as yet unknown, are chiefly responsible for internal or external hydrocephalus, depending

upon whether the fluid secreted by the ventricle reaches the subarachnoid space. There is under these circumstances either an increased secretion or a diminished absorption of cerebrospinal fluid. The symptoms attendant upon infections of the meninges with the pouring out of an exudate (bacterial meningitis) or of meningeal irritation without infection (aseptic meningitis, meningism, serous meningitis, marked meningeal or cerebral congestion) are in great part due to the increase of cerebrospinal fluid (secondary hydrocephalus). There is also an accumulation of toxic products of brain catabolism and bacterial growth due to fluid stasis, plus the added symptoms of general intoxication after the disease has become systemic. Pressure may be increased to such an extent by large hemorrhages into the ventricle or the subarachnoid space or into the brain or cord substance that coma may rapidly ensue. Release of pressure often causes a rapid clearing of the symptoms provided there has not been too great a degree of brain destruction and if a vital physiological area has not been involved. E. A. Graham³⁰ has reported a case of polyuria with marked increase of intraspinal pressure of unknown origin, rapidly cured by diminution of pressure by lumbar puncture. The frequency of polyuria in lesions of the base caused Cushing³¹ to advance the view that pituitary disturbance was at the bottom of the condition. Lewis and Matthews³² concluded from experiments that the polyuria was probably dependent upon hypersecretion of a diuretic substance elaborated by the posterior lobe of the pituitary, which is secreted by the pars intermedia. The favorable influence of spinal drainage suggests the possibility of increased intracranial pressure with the coincidental factors of increased secretion or delayed absorption of cerebrospinal fluid playing a part.

* In acute alcoholism, delirium tremens, uremia and other intoxications of known or unknown origin, increased pressure exists and may give rise to marked symptoms. In general paresis, especially late in the disease, the atrophy of the brain is accompanied by an increase in fluid, and it seems likely that in many of these cases an alteration of the histological structure of the choroid plexus may be looked for; so, too, in chronic thickening of the cerebral vessels in senility. Tumors of the brain are usually accompanied by increased pressure. This is due not so much to the encroachment of the cranial cavity by the tumor growth—which may become a factor if the tumor is large and does not encroach upon or erode cerebral tissue—as to the secondary hydrocephalus produced. As Frazier emphasizes, “the amount and rapidity of absorption is in proportion to the total amount of subarachnoid space available.” In tumors of the posterior fossa there is great intracranial pressure. This implies a larger quantity of cerebrospinal fluid, which by compression of the venous channels delays absorption. This causes the midbrain to be filled by blocking the isthmus of the tentorium, preventing the passage of fluid from the posterior to the anterior fossa. For this reason subtentorial tumors, because they interfere especially with absorption, first give rise to pressure symptoms. Brain tumors may occur without signs of intracranial pressure (vomiting, choked disk and headache) provided there is little or no disturbance of secretion or absorption.

Influence of Hypertonic Solution on Cerebrospinal Pressure.—Weed and McKibben in 1911 showed that it was possible to decrease cerebrospinal fluid pressure by the intravenous injection of hypertonic solutions. This work has since been confirmed by numerous clinicians.

Haden administered concentrated (40 per cent.) glucose in meningitis, with beneficial results, and Cushing and Foley demonstrated that the use of hypertonic solutions intravenously diminished pressure and brain volume. Weed and McKibben also used hypotonic solutions to increase brain volume and increase spinal fluid pressure, and it was shown by Cushing that hypotonic solution into the gastrointestinal tract had a similar effect. Sachs and Belcher lessened increased intracranial pressure caused by a brain tumor by the intravenous injection of 100 c.c. of a 35 per cent. solution of sodium chloride.

It has been found possible in many instances to cause decrease in intracranial pressure by the use of hypertonic solutions—sodium chloride, magnesium sulfate, glucose—per rectum, without many of the by-effects of intravenous injections. Fay pointed out the value of hypertonic magnesium solution by mouth in reducing intracranial pressure. Howe¹⁴⁰ experimented with various hypertonic solutions in cats and concluded that sodium bromide, calcium lactate, calcium chloride and magnesium sulfate were too toxic for use. Sodium citrate, sodium tartrate and sodium bicarbonate were ineffective. Sodium sulfate, sodium chloride, concentrated Ringer-Locke solution and concentrated tyrode solution and glucose produced satisfactory results. Sodium sulfate was shown by Weed and McKibben to have caused death after being satisfactory at first, and is unsafe. Sodium chloride produced the greatest decrease in intracranial pressure, but is toxic unless administered slowly. It is later mobilized in the tissues and produces a secondary wave of edema, as shown by Fay, and Howe concludes it is unfit for general clinical use, which objection he states applies to Ringer-Locke and tyrode solutions though they are less toxic. Howe concludes that glucose is the only substance of the group which is nontoxic and produces satisfactory depression of pressure.

Morrissey concludes that magnesium sulfate in 45 gram doses does not reduce pressure in two hours when given into the intestinal tract, but that the brain pressure undergoes the same dehydrating effect as the other tissues after its use, with a depression of general blood pressure, while sodium chloride intravenously effectively reduces pressure. Magnesium sulfate for the relief of intracranial pressure due to trauma was first advocated by Dowman, in 1922. Morrissey failed to obtain good results in clinical cases by the use of magnesium sulfate as advocated by Dowman and Fay. Forty-five grams of the crystals were given by mouth, repeated every four hours, if necessary. If impossible to give by mouth, it was administered in doses of 90 grams in 178 c.c. of water, by rectum, every four hours.

Functions of the Cerebrospinal Fluid.—The physiological data cited concerning the secretion and absorption of the cerebrospinal fluid are perhaps more or less certain, although some believe the main problems in this mechanism are still unsolved. In attempting to describe the function of the fluid we tread upon very uncertain ground. Even with the knowledge so far ascertained by numerous physiologists as our guide, our opinion can be said to be more or less speculative rather than scientific.

The brain and cord are enclosed within the rigid, unyielding confines of the skull and vertebræ and are of a soft, yielding texture capable of great compression, though at the peril of the physiological activity of

these vital organs. Indeed, it is safe to predict that without means of adequately protecting the nervous tissue of the brain and cord from the innumerable mechanical insults and commotions incident to the life of the individual, the delicate functions of these parts could not for long be carried out. Surrounded on all sides by the cerebrospinal fluid under a fairly constant pressure and suspended by the membranes and their prolongations from the bony envelope, the brain and cord are protected in their unyielding surroundings as if by a water-bed; further, the fluid filling up every nook and corner of the cranial cavity interpolates itself into every tiny space between the convolutions of the cortex and between the various lobes, in fact, filling all the free area unoccupied by nervous tissue and vessels, serving also in a measure to adjust the mechanism of the circulation of the nerve cells.

It would seem that there can be little doubt of this mechanical function of the cerebrospinal fluid. When the processes of secretion and absorption are nicely balanced, the nervous tissue and blood vessels adjacent thereto are subject to a uniform support at a certain pressure varying within physiological limits. Once these functions are disturbed, whether by an increase of secretion or a diminution of absorption, the anatomical relations of the parts are disturbed and their physiological activities altered. Under special abnormal conditions we have the subjective and objective disturbances of increased intracranial pressure and the attendant phenomena of headache, vomiting, choked disk, etc.

Protection Against Infection.—Has the spinal fluid any protective value in guarding against infection of the central nervous system? Under normal conditions, as already pointed out, the choroid plexus acts as a very efficient barrier to the entrance of most toxic substances into the fluid. Ordinarily, even in disease, the choroid gland prevents the entrance of bacterial or other organisms and their toxins into the spinal fluid. In certain septic states a positive blood culture may be obtained, indicating a general infection with a sterile spinal fluid. However, under certain conditions of disease the permeability of the choroid gland may be disturbed. Organisms or toxins enter and disease of the central nervous system may in this way occur, but whether infection usually occurs as a result of this invasion we cannot definitely say. Indeed, it is as likely that infection of the neuraxis occurs by direct extension from near-by foci of infection or by lymphatic or blood stream implantation without primary involvement of the cerebrospinal fluid. For example, we know that abscess of the brain may occur with a sterile fluid. According to Kafka,³³ the cerebrospinal fluid acts with the choroid plexus in preventing infection and creates certain hypothetical ferments which act in this capacity. Another method of infection of the cerebrospinal fluid would be the occurrence of metastatic foci anywhere in the central nervous tissue contiguous to the membranes, with infection of the membranes and direct infection therefrom of the cerebrospinal fluid. The integrity of the choroid cells may be disturbed by an overwhelming infection with damage to the histological structure of the gland and the entrance of toxic substances into the cerebrospinal system, or this integrity may be disturbed by lumbar puncture or by intraspinal injection, as has been pointed out recently by Flexner and Amoss.³⁴ Under normal conditions the choroid plexus acts to shut off from the nervous system harmful agents of one sort or another; in disease the relations

of this gland may be so changed that it becomes permeable to a greater or less degree, not only to the toxins and virus of disease, but also to whatever neutralizing or immunizing substances they may be giving rise to.

The cerebrospinal fluid may possibly serve as a means of dissemination of the product of pituitary activity (Cushing and Goetsch²⁵) and possibly also of that of the pineal gland. The rôle played by the cerebrospinal fluid in the distribution of these internal secretions is, as yet, obscure.

Is the spinal fluid the lymph of the central nervous tissue? As the circumambient medium between the cells of the nervous tissue on the one hand and the capillaries on the other, does the cerebrospinal fluid act as a medium of metabolic exchange, bringing to the tissues the chemical substances necessary for the maintenance of life (O_2 and energizing substances) and taking away those excretory substances, the result of tissue change and destruction inimical to life (CO_2 and waste matter), as Mott stated?

The lymph of the body is exuded through the thin-walled capillaries under certain conditions of osmosis and filtration and is similar to plasma, although poorer in its protein content. It conveys nutritive material and oxygen to the tissues and takes away waste matter and carbon dioxide and, in order to do so, must freely communicate with the blood vessels and the permeable membrane must be penetrable in both directions, as Halliburton has pointed out. True lymphatics have not been conclusively demonstrated in the cerebrospinal system. The perivascular and perineural spaces are filled with cerebrospinal fluid, and it has been argued that as the cerebrospinal fluid is the only fluid coming in contact with the cells of the central nervous system, it must be the medium of exchange between these cells and the blood. Although the cerebrospinal fluid does contain waste matter—as a description of the physical and chemical characteristics of it will show—it cannot, however, be claimed that it possesses any other similarity to lymph, and instead of being an exudation from the blood, it has been shown pretty conclusively to be a true secretory product of the choroid plexus; and while freely entering the blood in its exit it is not freely secreted from the blood. Halliburton, on the other hand, speculates that the sensitive neurons must be bathed in an ideal physiological saline solution in order to maintain their osmotic equilibrium. This is provided by the cerebrospinal fluid. The faint traces of protein in the fluid as compared with the larger amount in true lymph are sufficient for nutrition and are possibly just the kind of protein to repair the slight amount of wear and tear due to nerve action. The sugar present serves as a supply of energy. In the present state of our knowledge it must remain a moot point whether the cerebrospinal fluid acts as the lymph of the tissues of the brain and cord with the probability that this function is subserved in some way, as yet unknown to us.

PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE CEREBROSPINAL FLUID

Color.—SIGNIFICANCE OF BLOODY AND TURBID FLUIDS.—(a) In the normal individual the cerebrospinal fluid obtained by lumbar puncture

is colorless and quite clear, occasionally containing a few fine flocculi or tiny tissue shreds. It is odorless and has no taste, and under normal conditions does not coagulate. Occasionally the fluid may be faintly tinged with blood, due to trauma of a vessel during the passage through the epidural space before the membranes are pierced, or of a vein after the membranes have been punctured. If the amount of blood is very small the color may simulate very closely that of a slightly turbid fluid, from which it may be easily differentiated by microscopic examination. If the bleeding is considerable in amount, the fluid may be frankly bloody. The viscosity of the fluid is slightly greater than that of water, as may be noted from the following observations:

Borelli and Datta	1906	1.059	1.049
Galetta	1908	1.008	1.024
Levi Valersi	1911	1.006	1.105
Polányi	1911	1.020	1.027
Levinson	1919	1.0121	1.0489

In severely jaundiced individuals, the cerebrospinal fluid may be tinged yellow and is to be differentiated from the lemon-yellow color of xanthochromia, which will be considered in detail below.

(b) Under abnormal conditions the fluid may be bloody or turbid. In hemorrhages into the ventricles or brain substance contiguous to the membranes, the fluid may be decidedly bloody or possess varying degrees of color, from the bright red of fresh blood to the faint brownish or light yellow color indicative of old hemorrhage. A fluid of this type when centrifuged does not become clear, but is more or less tinted with old dissolved hemoglobin unless the hemorrhage is very recent, in which event it must be differentiated from a fluid containing blood due to the puncture. In the latter, the blood is precipitated by centrifugation, leaving a clear supernatant fluid. If vessels have been injured in the excursion of the needle before its entrance into the subarachnoid space, the blood issues slowly from the needle, drop by drop, and coagulates rapidly in the test tube like the blood obtained from the puncture of a blood vessel. If the hemorrhage is from one of the vessels of the brain or cord, due to trauma or rupture of an aneurysm, the cerebrospinal fluid issues under considerable pressure and is blood-tinged or decidedly bloody, depending in degree upon the amount of trauma, the time elapsed since the bleeding started, and the size of the hemorrhage. Usually when the bleeding is due to damage by the needle to a small vein and occurs into the subarachnoid space, the fluid is only faintly blood-tinged and gradually becomes clearer and finally macroscopically clear, especially in the last of two or three test tubes, although it is possible almost always to obtain a few cells microscopically, even in the apparently clear tube. Occasionally the cerebrospinal fluid in the lower part of the subarachnoid space is thoroughly mixed with blood from such an accidental vessel trauma, and clear fluid cannot be obtained. In this event it is advisable to puncture again a few days later in order to obtain a clear specimen; or the next higher inter-space may be tried.

In inflammatory conditions of the meninges due to microbial infection, the fluid is usually not clear, the degree of turbidity varying from the slightest stained-glass opalescence to the almost opaque turbidity of a purulent exudate, depending upon the stage of the disease and the

type and severity of the inflammation. In certain inflammatory conditions where there is mild meningeal exudation or where the lesion is limited to a comparatively small area—as in tuberculous meningitis—or where the inflammatory process is a chronic one—as in most of the syphilitic diseases involving the meninges—the fluid may be clear. In inflammatory conditions involving the brain or cord tissue with but little or no meningeal involvement, the fluid is usually clear or, in the event of meningeal irritation, slightly opalescent. In purulent processes of the membranes the exudate may be pocketed or walled off and clear fluid may be obtained by lumbar puncture. In purulent exudation in the ventricles not communicating with the subarachnoid space, the spinal fluid may be clear, while the ventricular fluid is turbid. Pus in the epidural space (extradural) from disease of the bone or from metastatic abscess in this region may issue from the needle which the operator may think is in the subarachnoid space—thus simulating a purulent spinal fluid, as in a case seen by the author.

XANTHOCHROMIA OF THE SPINAL FLUID; THE SPINAL FLUID SYNDROMES OF NONNE AND FROIN; COMPRESSION SYNDROME.—A yellowish color of the spinal fluid may be due to dissolved hemoglobin as a result of hemorrhage into the subarachnoid space, with tinting of the spinal fluid, the depth of color being due to the amount of hemorrhage and the length of time the hemorrhagic fluid has existed in the subarachnoid space before withdrawal. Such fluids are rich in hemoglobin and contain considerable protein, especially soon after the bleeding, and usually the presence of red cells and white cells, fresh or disintegrating, can be determined by microscopic examination.

This type of yellowish fluid is to be differentiated from *true xanthochromia*, not the result of hemorrhage, but definitely due to an isolation of the lower portion of the subarachnoid space, separating it completely from the upper part, and usually indicative of spinal cord tumor of the lower dorsal or lumbar region, causing compression. The identical findings have been recorded as a result of obliteration of the continuity of the subarachnoid space at some point, with an isolation of the lower from the upper part, by inflammatory lesions.

Froin,³⁶ in 1903, first described the condition in three cases, the chief characteristics of which were yellowish fluid (xanthochromia), increased cellular content and spontaneous, rapid coagulation on standing. About five years later, Nonne³⁷ reported three cases of spinal cord tumor with clear fluid, marked globulin increase, but without an increase of cells and without spontaneous coagulation of the fluid. In the opinion of Elsberg and Rochfort,³⁸ Nonne's syndrome is suggestive of extramedullary spinal cord tumor, while the Froin syndrome is characteristic of large endotheliomas or sarcomas which surround the conus or roots of the cauda equina. According to Hanes,³⁹ who has also reported a number of instances of this type of spinal fluid, the syndrome described by Nonne is merely an early stage of the fully developed syndrome described by Froin. In a case seen by the writer a very heavy globulin increase without pleocytosis, with clear fluid and a negative Wassermann reaction led to the discovery of a spinal cord tumor. In a case of tuberculous meningitis described by Leitch,⁴⁰ a thickening of the cervical membranes and adhesions caused the obliteration of the subarachnoid space. The fluid obtained was clear, limpid and yellow, coagulated

massively, did not contain tubercle bacilli, although they were found in the clear ventricular fluid. The presence of xanthochromia or clear yellowish spinal fluid, increased globulin content, spontaneous coagulation soon after withdrawal with or without some pleocytosis, is therefore indicative of compression of the spinal cord, but is no definite indication of the nature of the lesion causing the compression or the site of the lesion (Raven⁴¹). The diagnosis rests then on a consideration of all the data obtained by physical examination and examination of the spinal fluid. According to Elsberg and Rochfort, xanthochromia with increased lymphocytosis is characteristic only of large tumors of the conus and cauda equina, while Nonne's syndrome is more often found in compression of the cord at other levels. Xanthochromia, spontaneous coagulation and high cell counts point to disease in the lower dorsal or lumbar regions.

The color of xanthochromia is a light lemon-yellow which does not change from day to day, while the tinting due to hemorrhage is often a more marked amber-yellow and gradually fades away after repeated tappings. Hemoglobin can usually be detected in such fluid if red cells or their ghosts cannot. In true xanthochromia in the fully developed syndrome, the fluid coagulates spontaneously within a few hours after withdrawal and the globulin increase is stationary and marked. It is agreed that fluid stagnation is essential to the syndrome and that transudation of plasma from the vessels in the isolated cul-de-sac causes the peculiar color and globulin increase.

Sprunt and Walker⁴² reviewed some 100 cases from the literature all of which were studied at operation or autopsy, and all of which showed obstruction in the subarachnoid space. Some of the conditions responsible for the obstruction, besides tumor of the spinal cord, were tuberculous spondylitis, intradural tuberculous granuloma, extensive adhesions between cord, arachnoid and dura in meningomyelitis and gamma of the meninges. Extramedullary tumors as a rule gave a lower cell count than intramedullary tumors, in their opinion. Of 24 cases of extramedullary spinal tumors, 41 per cent. had xanthochromia while in 12 cases of intramedullary growth xanthochromia was never noted nor was it found in any cases of extradural neoplasm.

Electrical Conductivity.—Little work has been done on the electrical conductivity of the cerebrospinal fluid. Examinations have been made by Polányi,¹⁴¹ Levinson,¹⁴² Eckel,¹⁴³ and by Crile, Hosmer and Rowland.¹⁴⁴ Eckel made tests on some 360 fluids obtained from normal and abnormal conditions, and concluded that the conductivity depends upon the total ionized solids of the fluid which is composed chiefly of sodium chlorides and other electrolytes. The protein content of the fluid retarded conductance. In conditions with marked meningeal reaction, particularly tuberculous meningitis with low chloride content, there was some departure from the normal to which most other conditions conformed. His figures for maximum normal were 0.01549, minimum 0.01446, at 25° C. Levinson's figures were 0.0141 to 0.01365 at 20° C.

Specific Gravity.—The specific gravity of the cerebrospinal fluid varies from 1.003 to 1.009, both in health and disease. In the purulent fluid of inflammatory meningitis the specific gravity tends to approach the higher figure. The following table from Kopetzky⁴⁵ gives the specific gravity in a variety of abnormal conditions:

490 CEREBROSPINAL FLUID IN HEALTH AND DISEASE

Normal fluid	2	specimens, 1.006—1.007
Delirium tremens	7	" 1.003—1.006
Typhoid fever	1	" 1.006
Tuberculous meningitis	6	" 1.001—1.007
Meningococcic meningitis	4	" 1.007—1.009
Purulent (otitic) meningitis	4	" 1.001—1.007
Anterior poliomyelitis	5	" 1.007—1.008
Cerebellar (tbc.) tumor	1	" 1.006
Meningism	3	" 1.006
Cerebral embolism	3	" 1.004—1.008
Chronic hydrocephalus	3	" 1.006—1.007

Reaction.—The reaction of the cerebrospinal fluid is practically neutral and the H-ion concentration is almost equal to that of the blood serum. Bisgaard ⁴⁴ gives the pII value as 8.10. Weston ⁴⁵ gives the average figures as 8.12. The presence of amphoteric amino-acids and proteins tends to preserve a neutral reaction in the fluid. According to Felton, Hussey and Bayne-Jones, ⁴⁶ the organic constituents vary considerably in the cerebrospinal fluid, being generally less than in the blood. The hydrogen-ion concentration is most intimately related to the dissociable carbonic acid contained in the fluid. They gave as the average figure pII 7.75 with variations from 7.4 to 7.9, and the average alkalinity from 0.4 to 0.6. This is due to the presence of phosphate, carbonates and bicarbonates. These examinations were made immediately after withdrawal of the fluid before any change could take place—a factor of importance in getting accurate determinations. Fluids become more alkaline on standing. Israelson and Krizman found the pII value at 37° C. to be 7.35 in normal fluids, and tested 136 cases in individuals with various manifestations of syphilis and concluded that the concentration of the hydrogen-ion has a great influence upon the outcome of the tests for syphilis. As the concentration of the hydrogen-ion increases, or as the value of pII decreases, there is an increasing percentage of positive reactions in the cerebrospinal fluid. For example:

pH	Globulin and Cells	Wassermann Test	Mastie
7.7	1.25%	5.0 %	8.75%
7.6	40.00	26.66	46.66
7.5	71.43	67.85	78.50
7.4	81.25	93.75	100.00

McQuarrie and Stohl, ¹⁴⁵ in comparing the pII of the blood and spinal fluid, showed that both have the same values, viz., pII 7.35 to 7.40, with a possible error of 0.02. These authors have published a new colorimetric method for the determination of the pII of the spinal fluid which takes into cognizance the fact that there must be no loss of CO₂. According to Mestrezat, the alkalinity of the fluid equals 1.25 to 1.30 grams sodium carbonate to the liter, as tested with phenolphthalein. According to Mott, ⁴⁷ the reaction varies slightly in the various diseases of the central nervous system, and is practically the same as during health. Most workers agree with this view, although Hurwitz and Tranter ⁴⁸ found the average normal 8.11 and the average for syphilitic fluid 8.14.

Inorganic Constituents.—The cerebrospinal fluid consists of water to the extent of 989.54 parts out of 1,000, the remaining 10.45 being solid matter (Zdarek ⁴⁰). The mineral matter in 1,000 c.c. equals about 8.73 grams and consists principally of sodium chloride.

THE CHLORIDES.—The chlorides in the spinal fluid are fairly constant in quantity, between 0.72 and 0.75 per cent., calculated as sodium chloride. According to Greenfield and Carmichel, readings above 0.75 per cent. indicate renal deficiency, while lower readings than 0.70 per cent. point to meningitis. While the figures may be normal even in marked degrees of acute nephritis, high figures in the fluid in a case in coma should make the examiner suspicious of the functioning of the kidneys. In suspected cases of meningitis, a low chloride content—under 0.70 per cent.—is very suspicious of a spreading meningitic process, and often may help to differentiate in cases of brain abscess, brain tumor and polio-encephalitis associated with a high cell count, but in which the chlorides usually remain at the normal level. In acute meningitis the chlorides may descend as low as 0.65 to 0.68 per cent. and in tuberculous meningitis the figures may descend as low as 0.5 per cent. According to Mestrezat, this low chloride content is a diagnostic sign of tuberculous meningitis, second only to the presence of the tubercle bacillus.

It is important to bear in mind that the chlorides may be markedly lowered in acute lobar pneumonia, even without the presence of meningitis, so that in this condition the chloride content is of no value in differentiating between a true and a pseudo or serous meningitis. The same is true in such acute infectious diseases as typhoid and typhus fever and in generalized tuberculosis.

The remainder consists of traces of potassium and sodium carbonate phosphate and bicarbonate, sulfate and nitrate with minute traces of calcium, magnesium and iron oxides. Rosenbloom and Andrews determined the potassium content of the cerebrospinal fluid in 31 cases, and found that it was not increased in degenerative diseases of the cerebrospinal system. It is not possible, they believe, on the basis of potassium content to draw any conclusion in regard to the condition present in cerebrospinal syphilis. The calcium content of the cerebrospinal fluid was found by Halverson and Bergheim ⁴¹ to be constant at about 5 mg. to 100 c.c., which is about one half that of the blood serum, and in syphilis of the nervous system variations of not more than 0.1 to 0.3 mg. were found. Mestrezat, in 20 normal fluids, got 7.1 mg. of calcium per 100 c.c., while Schmidt (quoted by Halverson and Bergheim) obtained as high as 15.3 mg. in a hydrocephalic adult.

Organic Constituents.—The principal protein present in the cerebrospinal fluid are albumin and globulins. According to Hammersten, they are globulins and albumose, while Halverson thinks the proteins are principally nucleoproteins. Mestrezat identifies the protein as globulins and faint traces of albumin. The concentration of albumin to albumins and faint traces of albumin. The concentration of albumin to albumins in the spinal fluid, according to Delpech, is 0.14 to 0.04. According to Denis and Ayer, the amount of protein normally present in the lumbar fluid varies from 15 to 45 mg. per 100 c.c. but occasionally up to 80 mg. have been found in apparently normal fluids. The total protein content varies from 1.5–5 grams per liter and will be seen by the following table:

TOTAL PROTEIN CONTENT

	Per cent.
Quinke	0.2—0.5
Lenhartz	0.25
Pfaundler	0.2—0.4
Leri	0.5
Nonne and Apelt	0.5
Mott	0.3
Mestrezat	0.186
Nauratzki	0.22
Comba	0.19
Concetti	0.15—0.25
Marchand	0.06—0.2
Broder and Rodhain	0.25
Ayer and Foster	0.25

An exact qualitative and quantitative analysis of the protein content of the cerebrospinal fluid in normal cases is yet to be made. Most determinations show at least a 5 per cent. error. The exact origin of protein found normally in the fluid is unknown. In certain abnormal conditions—inflammatory, degenerative and irritative—affecting the neuraxis and its membranes, the protein content of the fluid is more or less markedly increased. This increase can be detected by an examination of the fluid and is of much diagnostic significance.

As laboratory methods for the determination of protein in the cerebrospinal fluid become more accurate and less complicated, slight variations in the protein content become more significant. By the newer diagnostic methods of ventricular and cisternal puncture comparisons of these fluids with the lumbar fluid often point to the location in the central nervous system of the disease process. Ventricular fluid contains little protein normally—as low as 5 mg. per 100 c.c. Fluid from the cisterna magna contains more, but less than that of the spinal fluid. Spinal puncture at various levels may show decided variations in the protein content; and changes in the appearance of the fluid point to the level of the disturbance.

The proteins in the fluid are increased in proportion to the degree of inflammatory reaction in the membranes. In acute meningitis the proportion of albumin to globulin is as 12 to 1 (Eskuchen). This high proportion prevails also in arteriosclerosis, while in general paresis the proportion of increase is as 7 to 3. In spinal cord tumor it may be 2 to 1. As the inflammatory process wanes the protein content decreases. Meningeal irritation, especially if accompanied by great increase in cells, may show a moderate increase in protein content due to cellular degeneration, but the amount is never as great as in true inflammatory lesions. Vascular changes contiguous to the membranes rarely show more than a slight increase, if any, in the protein content. Such slight globulin reactions may occasionally be found in multiple sclerosis, epilepsy, chorea, brain tumors, abscesses and vascular syphilis, and hence the importance of considering protein increase in relation to the clinical picture and the outcome of the other tests. With a very great increase in protein, and few, if any, cells, with or without change in color of the spinal fluid, the

possibility of compression of the cord must be considered.* Occasionally marked increases are found in brain tumor and cerebral arteriosclerosis.

Lactic acid, produced by the disintegration of glucose, is found in traces in normal spinal fluid. Its presence can be determined qualitatively by the use of Uffelmann's reagent (5 per cent. Fe_2Cl_6 , 1 part and 1 per cent. phenol—5 parts). The relation of normal spinal fluid lactic acid to that of the blood is about 60 to 90 per cent. In quantitative determination of lactic acid either the sulfuric acid method of Clausen¹⁴⁶ is recommended, or the method of Schaller.¹⁴⁷

The normal figures for the spinal fluid vary from 8 to 10 mg. per 100 c.c. A marked increase is found in acute meningitis, and to a lesser degree in eclampsia, uremia, hydrocephalus, and brain abscess, while in cerebrospinal syphilis the figures are not increased. In brain tumor there is frequently a moderate increase above normal.

Choline is present in normal fluid in minimal traces (Kopetzky, Haliburton, Gumprecht⁶³ and others), and is a product of brain metabolism, probably due to the decomposition of lecithin. According to Kopetzky, there is in the meningitides especially a decomposition of the lecithin molecular element of the nervous tissues with the production of increased amounts of choline in the cerebrospinal fluid. To this he attributes the toxic effects of the disease. The interference with the free circulation of the cerebrospinal fluid, due to increased pressure, results in an accumulation of this toxic substance with a poisonous effect upon vital nervous centers.

The principal *carbohydrate* present in the cerebrospinal fluid is dextrose. Until recently there was considerable doubt as to the nature of the reducing substance present in the cerebrospinal fluid. Haliburton thought it was a substance akin to pyrocatechin, while according to Nawratski,⁶⁴ Zdarek⁴⁰ and Rossi,⁵⁵ the substance is dextrose. Schloss and Schroeder,⁶⁶ in a recent article, have proven that the reducing substance is a fermentable dextrose-rotary sugar, probably dextrose, and that in infants and children the amounts range from 0.05 to 0.124 per cent., approximately the same as the sugar content of the blood. Kraus and Corneille⁶⁷ found the average to be 0.08 per cent., the range from 0.055 to 0.110 per cent. Leopold and Bernhard⁵⁸ found the average amount to be 0.07 per cent. Hydrolysis of spinal fluid filtrates by Fremont-Smith and M. E. Dailey showed that the spinal fluid sugar values decreased from 1 to 15 per cent. after being subjected to the method of Folin and Berglund, thus proving that not all the reducing substance is dextrose. The sugar content of the ventricular fluid is somewhat higher than in the lumbar fluid. The blood sugar is always higher than the spinal sugar.

In certain inflammatory conditions of the meninges, especially those of bacterial origin (*Diplococcus intracellularis meningitidis*, pneumococcus, streptococcus, tuberculous, staphylococcus, etc.), the sugar content of the fluid is diminished at the onset of the disease and soon is entirely absent from it. The quantity may be below 50 mg. per 100 c.c. Coincident with the decline of the inflammatory process, the sugar in the fluid commences to return, so that this fact has been used as an index

* An admixture of even a small amount of blood, due to the result of the tests for protein—a fact to be kept in mind when considering the significance of decreased globulin or albumin.

of recovery. In meningism of pneumonia and typhoid fever and in the serous meningitis of delirium tremens and uremia, and frequently in tuberculous meningitis the sugar content is normal; and in the first named conditions this fact may be of differential diagnostic value in ruling out a true inflammatory condition of the meninges. Sugar may be increased in epidemic encephalitis (above 80 mg. per 100 c.c.) and in diabetes mellitus, occasionally in nephritis and, according to Mestrezat, in uremia and toxic pneumonia and typhoid, and in various organic nervous diseases coincident with a hyperglycemia a high sugar content in the fluid may be recorded. In diabetes mellitus the sugar in certain instances may be accompanied by acetone, diacetic acid and oxybutyric acid, especially if coma is supervening. The sugar content of the fluid is practically unchanged in the various organic and functional diseases of the central nervous system, other than those mentioned.

Cholesterol is present in the spinal fluid in traces, the average amount being greater in certain degenerative types of disease of the central nervous system, e.g., general paresis. But the variations, according to Weston,⁶⁰ do not bear any constant relation to the type of psychosis present.

CHOLESTEROL CONTENT OF THE CEREBROSPINAL FLUID IN VARIOUS PSYCHOSES

	Average age	Quantity	Mg. per c.c.
Paresis	43	179	.003965
Senile dementia	72	127	.0037
Organic dementia	71	173	.00496
Manic-depressive insanity.	54	143	.00305
Dementia precox	42	118	.00451
Cerebrospinal lues	54	160	.0064
Epileptic psychosis	42	141	.00467

Urea is present in the normal fluid in quantities identical with those of the blood, varying from 0.01 to 0.05 per cent. (Soper and Granat⁶⁰). In conditions of uremia the urea content rises coincident with a rise of the urea content of the blood. A spinal fluid content higher than 0.2 per cent. urea indicates a severe uremia and a rapidly fatal termination (Soper and Granat). In cases of nephritis a urea content between 0.1 and 0.2 per cent. means a rapidly fatal termination in the majority of cases. A content of urea between 0.05 per cent. and 0.1 per cent. is suggestive of a severe urea retention, but definite conclusions cannot be drawn from a diagnostic or prognostic standpoint without a consideration of the clinical condition of the patient. In acute nephritis without uremic symptoms, Leopold and Bernhard⁵⁸ found the total non-proteid nitrogen slightly increased and uric acid present in small amounts, while in acute nephritis with uremic symptoms the total non-proteid nitrogen, urea and creatinin were markedly increased, the uric acid slightly increased, although the figures were somewhat lower than in the blood. These studies were made on the spinal fluid of children. These authors found the total nonproteid nitrogen to average 21 mg. per 100 c.c., the urea nitrogen 9.9 mg. per 100 c.c., creatinin 0.9 mg. per 100 c.c., while uric acid was present in amount insufficient for quantitative analysis. They found the total nonproteid nitrogen of the spinal fluid to be about 75 per cent. of that of the blood; urea, 82 per cent.,

and creatinin, 60 per cent. In serous meningitis the nonprotein nitrogen and sugar were found to be normal, while in tuberculous meningitis the figures were normal, with the exception of creatinin, which was slightly increased.⁶¹ Rosenbloom,⁶² in an examination of 200 c.c. of cerebrospinal fluid from different cases, using the method of Jaffe, failed to find any trace of creatin or creatinin in the spinal fluid.

TECHNIC OF LUMBAR PUNCTURE

Spinal puncture, if properly and skilfully performed, with the necessary safeguards and precautions, is a simple procedure. It is usually attended with slight or no pain to the patient, and the operation carries with it, in the vast majority of instances, no danger to life. The after-effects of the puncture are frequently headache and, occasionally, dizziness and vomiting. The headache can be mitigated to a certain extent but cannot always be entirely avoided. There may be some pain in the region of the puncture site due to trauma to the tissues traversed by the needle, especially if numerous punctures have been made before entering the canal. The headache disappears promptly, as a rule. Occasionally if the needle is not directed in the proper axis the nerve-roots may be traumatized, usually with momentary pain along the sensory terminals in the thigh, leg or foot. The motor roots are not often affected, but involvement of the sphincters and of the lower extremities has been described.

In a few instances the simple withdrawal of not more than 5 c.c. of fluid has aggravated the existing sensory symptoms, especially in cases of syphilis of the central nervous system, but the pain can easily be controlled by the administration of an opiate. In over fifteen years' experience in spinal puncture work, the writer has seen one fatality which occurred six hours after puncture and which could not definitely and surely be attributed to it--and knows of no instance where the patient was harmed permanently by the operation. Indeed, aside from headache, which is usually mild, though occasionally severe and agonizing and lasting from a few days to a week or two, ill effects have rarely been observed if proper precautions were taken.

The majority of cases of *sudden death following lumbar puncture* have occurred in patients with tumors of the cerebrum or cerebellum. Cramer⁶² lists 38 cases, as follows:

Cerebral tumors	16
Cerebellar tumors	11
Cerebellar tubercle	1
Uremia	2
Tuberculous meningitis	2
Cerebrospinal meningitis	1
Cerebellar aneurysm	2
Sylvian artery aneurysm	1
Hydatid cyst	1
Hydrocephalus	1

The occurrence of sudden death in cases of intracranial neoplasm is not unknown, so that undoubtedly some cases of death following punc-

ture, especially after a few hours have elapsed, have probably not been due to the puncture. Where initial symptoms of respiratory embarrassment ensue soon after puncture and end in death, foraminal hernia with embarrassment of medullary circulation may be assumed to be the cause of the fatality. In individuals with diseased cerebral vessels

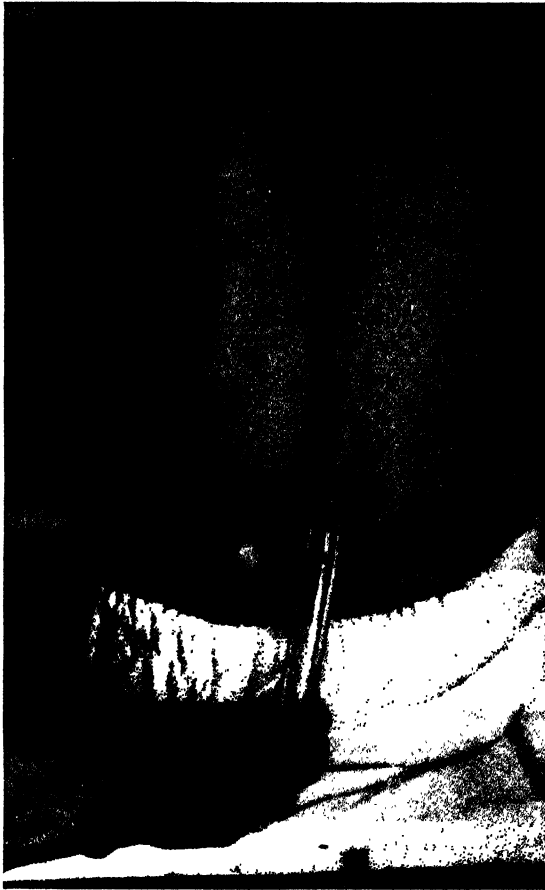


FIG. 1.—LUMBAR PUNCTURE: SITTING POSITION.

Patient's back bent slightly forward, chin upon breast, supported by nurse. Needle in spinal canal. Skin over vertebral spines and crests of ileum painted with tincture of iodine to outline position of puncture site.

sudden withdrawal of fluid may lead to rupture--apoplexy. Thus it behooves the physician to enter upon his work advisedly, with every precaution, and with a full realization of possible dangers.

The practitioner can easily become proficient in puncturing the spinal canal by attention to the details of the procedure, as described below. A study of the position of the lumbar spines and laminae on the skeleton, in relation to the spinal cord and its membranes, and practice on the cadaver are recommended.



FIG. 2.—LUMBAR PUNCTURE: RECOMMENDED POSITION.

Patient on operating table, thighs neatly flexed on abdomen, back arched forward. Nurse flexing thighs of patient and supporting its chest and head. Needle in position, crests of ileum outlined by fracture of nodine markings.

Position of the Patient.—The procedure can be accomplished with the patient in the recumbent position, on his side, or sitting up on a stool or at the edge of a bed or operating table (Fig. 1). The writer prefers the former position for the vast majority of cases. In patients on whom the puncture is to be done for diagnostic purposes, especially if there is any possibility of a tumor of the pons or lesion in the neighborhood of the medulla or pons, the decubant position should be chosen and the spinal manometer should be used to control the pressure during withdrawal of the fluid.

It is perhaps safest for the practitioner to adopt the reclining position as a routine, to avoid not only the danger of sudden death which has been known to follow the sudden release of fluid in the conditions mentioned, but also the lesser unpleasant complications alluded to above.

The patient is placed on the very edge of a firm, flat bed with his back parallel to the edge, thighs and knees flexed to the fullest extent, and the chin brought as far forward on the chest as possible by flexion



FIG. 3.—LUMBAR PUNCTURE: RECUMBENT POSITION.

Nurse with arm in patient's popliteal spaces, flexing thighs. Patient's back is parallel to edge of table. Needle in subarachnoid space, stylet withdrawn and fluid dropping slowly into sterile test tube. Note tincture of iodine markings for sterility of field of operation and as guide to landmarks.

of the neck and shoulders (Fig. 2). An effort should be made to keep both shoulders in a line perpendicular to the surface of the bed. It is quite important to have the surface of the bed flat and firm. A table leaf placed between the mattress and the spring will greatly facilitate the operation by preventing a sagging of the spinal column, throwing the interspinous space out of alignment by a partial rotation of the vertebrae. An assistant should place one hand behind the patient's head and the other arm should firmly grasp both popliteal spaces, flexing the legs and thighs upward, doubling the patient up in the Jack-knife position, in order to widen the interspinous spaces as much as possible. Care should be taken not to allow the shoulders or chest to sag away from the operator who stands facing the patient's back, while the assistant should kneel in the bed or stand on the opposite side facing the operator (Fig. 3). In the hospital a flat operating table is preferable

to a bed. The exact position of the patient is a *sine qua non* for a rapid and successful puncture with the minimal amount of manipulation; hence the emphasis laid on details.

If the sitting position is preferred, the patient is made to sit upon a moderately low stool, with back bent forward slightly, the arms upon the thighs or the hands grasping the knees. An assistant stands in front of the patient and steadies the head and shoulders, or in the absence of an assistant the patient should sit with the head against a wall.

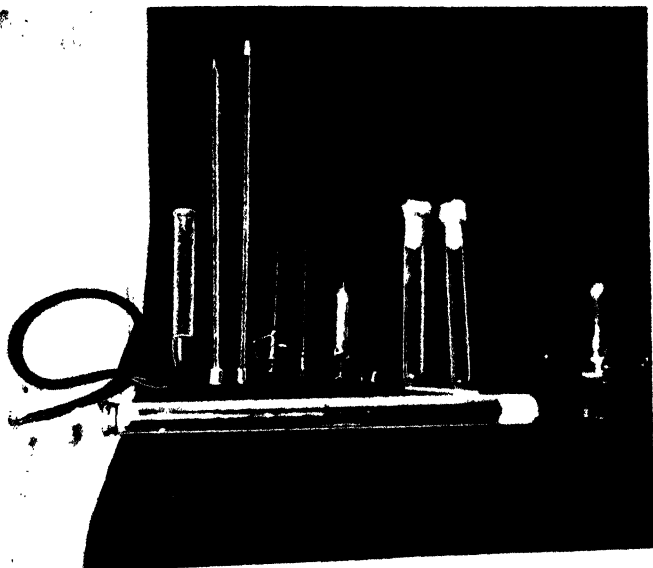


FIG. 4.—APPARATUS FOR LUMBAR PUNCTURE AND INTRASPINAL THERAPY.

Improvised injecting funnel. (2, 3) Manometer. (4, 5) Needles for puncture. (6, 7, 8) Record syringe and needles for local anesthesia. (9, 10) Record syringe. (11) Alcohol lamp. (Below) Catheter rheostat for preserving manometer tubes in alcohol for sterility.

Aseptic Precautions.—Strict asepsis is absolutely essential in carrying out the procedure. The needles used should be thoroughly beveled, the operator's hands should be scrubbed as carefully as for a major operation, or sterile gloves should be worn, and the field of operation surrounded by sterile towels. The skin at the site of puncture and for at least four inches about this site in all directions radiating should be coated with tincture of iodine. The crests of the abdomen should also be lightly touched with tincture of iodine to point out the landmarks.

Needles and Apparatus Necessary.—For the ordinary diagnostic puncture a moderately short-beveled left Lipp's pointed Quincke needle—preferably of nickeloid or nonbrittle steel and of about 34-1 mm. bore

and about 10-12.5 cm. in length, armed with a stylet, is necessary. In recent years the writer has been using a sharp pointed nickeloid needle of about 18 or 20 gauge B & S, for puncture. For children a 7.5-8 cm. needle of about 20 gauge (B & S) and about 10 cm. long is necessary. For very stout and muscular individuals a needle at least 10-12.5 cm. long is necessary. The needle should always be



FIG. 5.—LUMBAR PUNCTURE: INTRODUCTION OF THE NEEDLE.

Note forefinger of left hand pointing to interspinous space. Needle being introduced perpendicular to skin and parallel to plane passing through spinal column.

guarded by a stylet, which serves not only to keep the lumen free until the subarachnoid space is reached, but can also be used to regulate the flow of spinal fluid. There are a number of special needles on the market designed for the purpose of facilitating the withdrawal of fluid slowly, measuring the pressure of the fluid and providing means of easily and quickly attaching an apparatus or syringe for the injection of therapeutic sera. The apparatus of I. Strauss⁶³ is one of the simplest and best of these. It is shown in Fig. 8. By means of graduated withdrawal of the stylet the fluid can be made to ascend the measuring arm of the graduated manometer or allowed to drop slowly from an exit provided. To inject medicated fluids or sera this exit is plugged with a small stylet, the pressure manometer removed and the syringe

or gravity apparatus attached here. The whole apparatus is easily sterilized by boiling. The apparatus of J. M. Wolfsohn¹⁰ is an ingenious contrivance, being practically a Quincke platinum-iridium needle with a three-way stop-cock. A very small amount of fluid, about twelve drops, is needed for the reading of the pressure in the graduated manometer, and one of the arms of the cock can be used for the injection of fluids.

Frazier¹⁵ uses a needle with a three-way stop-cock attached, provided with a stylet. The pressure reading tube, which is small and can be conveniently carried in the pocket, is a mercury manometer and fits into one of the arms of the stop-cock. To those preferring a



FIG. 6.—LUMBAR PUNCTURE: INTRODUCTION OF NEEDLE.

Needle having been pushed through the skin is being moved gently forward into the subarachnoid space. Note position of hands and neck.

mercury manometer this apparatus is recommended. The writer prefers the water manometer, it being simpler and less expensive and just as accurate and reliable.

One of these types of apparatus is necessary if pressure readings are to be taken, although an inexpensive apparatus can be devised by purchasing a heavy manometer tube of 1 mm. bore, calibrating it for purpose and fitting it on one arm of a three-way stop-cock. In all cases where a tumor in the posterior fossa is suspected, it is advisable to use a manometer and to withdraw a very small amount of fluid, if examination of the fluid is necessary. The stop-cock should accurately fit the hub of the puncture needle. An expensive apparatus

for puncture and treatment can also easily be devised. A half-ounce glass catheter-tipped syringe or the barrel of a 20 c.c. Record or Luer syringe, to which twelve inches of rubber tubing is attached, and to the other end of which tubing is placed a small metal adapter to fit the hub of the puncture needle, serves as an injecting funnel (Fig. 4).



FIG. 7.—LUMBAR PUNCTURE: PRESSURE READING.

Needle in position with both tubes of manometer attached for pressure reading. Stylet of needle completely withdrawn and fluid mounting in calibrated tube.

Site of Puncture.—Ordinarily an imaginary line drawn between the crests of the ileum will intersect the spine at the proper level for puncture, i.e., just below the 4th lumbar spinous process. The needle is introduced in the midline (to avoid the roots of the cauda equina, which are about 2–5 mm. apart) exactly between the spinous processes of the 3d–4th or 4th–5th lumbar vertebrae or in the lumbosacral space. In

TECHNIC OF LUMBAR PUNCTURE

children the lower sites are preferable, for while in the adult the lowest portion of the cord rarely reaches beyond the 12th vertebra, infants the *conus medullaris* may occasionally reach the 11th lumbar vertebra. The terminal nerve roots making up the *cauda equina* branch off at an angle from the cord along the lumbar region, and the studies



FIG. 8.—LUMBAR PUNCTURE: PEN STYL READING—Caudal View

of Lusk⁶⁶ have shown that the only vertebral interspaces through which puncture of the subarachnoid space can be made with practical assurance that nerve structures will not be perforated, are the 4th lumbar or lumbosacral—preferably the former. In individuals with spondylitis of the lumbar vertebrae or marked curvature, allowance must be made for the alteration in the position of the interspace spaces in selecting the site for puncture and in the direction of the needle toward the canal. If there is a *cauda equina* lesion or if the subarachnoid space at the

level punctured is obliterated, it may be necessary to puncture at a higher level, going between the 3d or 4th, or 2d and 3d lumbar vertebræ. In one case in which puncture at the 4th lumbar space gave a dry tap, successive punctures in the higher spaces gave xanthochromic fluid, and finally clear fluid, and helped to localize the tumor subsequently removed by operation.

The Puncture.—The needle should be inserted midway between the upper and lower spinous process, perpendicular to the skin and parallel to the surface of the operating table or bed (Fig. 5). The needle is first grasped with the shaft between the thumb and index finger, with the hub resting against the center of the palm of the hand—in the position in which one grasps a shoemaker's awl—and pushed through the skin for about one inch only; then the palmar surface of the last phalanx of the index finger is placed on the hub cap of the needle, while the thumb and other fingers grasp the shaft of the needle near the hub and gently push it forward until the point is felt to pierce the membranes and pass into the subarachnoid space (Fig. 6). There will be a give to the needle as the membranes are pierced, and care should be taken not to use too much force, otherwise the anterior wall of the space will be touched and possibly one of the plexuses of veins ruptured, with consequent bleeding into the cerebrospinal fluid. Depending upon the musculature and obesity of the patient, the needle will have to be inserted from 5–10 cm. before this point is reached.* The stylet is now withdrawn slowly, and if the needle is in the subarachnoid space, fluid will be seen to issue from the needle (Fig. 3). If bony resistance is encountered before fluid is obtained, the needle should be withdrawn until within one inch of the skin and the direction of the needle altered slightly either upward or downward or laterally until the membranes are pierced. The needle must not be bent in an effort to change its direction, for fear of snapping it off. Sometimes the needle is in the canal but the lumen of the needle is obstructed by a bit of membrane or exudate or a nerve strand, so that before withdrawing it entirely the stylet may be inserted again and rapidly withdrawn to create suction to clear the needle, or it may be rotated on its axis slightly or very slowly withdrawn a few millimeters or pushed in a bit until fluid issues. When the stylet is withdrawn free blood may issue from the needle, due to hemorrhage from veins upon the membranes in the epidural space. The needle must then be entirely withdrawn, cleansed free of blood, and the patient punctured again. If the fluid issues blood tinged, the hemorrhage is subdural and the fluid usually becomes clearer as it flows, though it may not become wholly free from blood either macroscopically or microscopically. If it is absolutely essential to obtain a blood-free fluid, the patient should be punctured again in the space higher up. The needle having entered the subarachnoid space, it should be allowed to issue drop by drop into a sterile test tube. One to two c.c. are gathered in each of two or three test tubes and will suffice for all the necessary bacteriological and serological tests. If pressure readings

*The needle traverses the following structures in its excursion: skin, subcutaneous tissue, interspinous ligament, subflavous ligament, epidural fat, vein plexus, dura mater, arachnoid. In this region the dura and arachnoid are in contact while the pia invests the cord and nerve roots. The dural sac is between the arachnoid and the pia mater.

TECHNIC OF LUMBAR PUNCTURE



FIG. 9.—LUMBAR PUNCTURE: WITHDRAWAL OF FLUID

Needle in position. Manometer withdrawn; stylet inserted slightly to close this aperture, and fluid issuing into test tube from aperture from which stopper or chain has been removed.

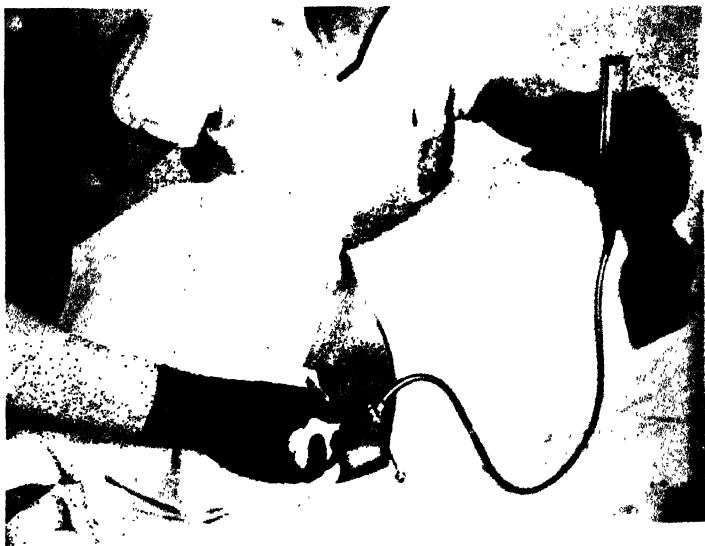


FIG. 10.—LUMBAR PUNCTURE: INSERTION OF TEST TUBE BY CATHETER. METHOD SHOWING APPLICABILITY OF FIG. 9.

are desired, the manometer is attached as soon as the needle enters the canal and before the stylet is withdrawn, the readings made, and the fluid in the manometer used for the examination. Where fluid is to be removed for therapeutic purposes or if the fluid is under greatly increased pressure, it is unwise to reduce the pressure below 100–120 mm. of water or 10–12 mm. of mercury. In using the needle to gauge the pressure for this purpose the fluid should be permitted to flow until it issues slowly drop by drop from the needle. When the pressure is high the fluid will issue in a spurt or steady stream if the point of the



FIG. 11.—LUMBAR PUNCTURE: INFLASPIGAL INJECTION, ANOTHER VIEW.

needle is free in the canal and unimpeded. It is of the greatest importance for the novice to be mindful of the danger of too sudden or rapid withdrawal of fluid in certain intracranial conditions, and in every new case so to regulate the flow of the fluid from the needle by means of partial withdrawal of the stylet from the hub of the needle, or by use of a pressure apparatus, that pressure will be reduced slowly.

The Queckenstedt Phenomenon.—Pressure on the jugular veins causes increased intracranial pressure, which can be recorded by means of the spinal manometer and can be charted graphically. Pressure on the jugulars by the finger or by a specially prepared band increases the pressure in the lumbar sac, which in turn increases the column of fluid in the manometer. Failure to cause this rise is indicative of a block somewhere between the cranial cavity and the site of puncture. This phenomenon was first used diagnostically by Queckenstedt.

TECHNIC OF LUMBAR PUNCTURE

Complete block is easily demonstrated by a failure of the fluid to rise promptly in the manometer, but in incomplete block there may be a definite rise, perhaps less promptly, with a hesitating and interrupted fall of the column of fluid as pressure is released on the jugulars. In cases where there is no block, even a slight touch of the jugular often causes a characteristic rise and prompt decline when pressure is released. Often in cases of block, jugular compression may be unproductive of a rise, but coughing or straining may cause a rise, due to increase of pressure in the intraspinal chamber.

Amount to Be Withdrawn.—For ordinary diagnostic procedures withdrawal of 3–5 c.c. is sufficient. If in cases of meningitis the fluid is clear and tuberculous is suspected, from 5–10 c.c. or more may be removed to facilitate the search for tubercle bacilli. In lucid individuals where the puncture is done for diagnostic corroboration in an individual not suspected of having involvement of the nervous system, it is wise to remove as little fluid as possible in order to avoid after-effects. Although individuals with involvement of the nervous system occasionally suffer from this, it seems that normal patients suffer more and oftenest, while paretics infrequently complain of after pains. Occasionally lightning pains in tabetics are aggravated for a short time after the withdrawal of fluid, or a crisis may even though rarely be provoked. In all these cases 2–3 c.c. of fluid will suffice for all diagnostic purposes. Replacement by saline has not proven of any value in the writer's experience. A safe guide in most cases is not to remove more than the amount indicated unless the fluid is under increased pressure, in which event it may be allowed to flow until pressure is reduced almost but not quite to normal, say to 150–130 mm. of water.

After-treatment.—To prevent entirely or mitigate the painful sequelæ of lumbar puncture, **rest in bed** after the puncture is essential. The foot of the bed may be raised a foot, in case tumor of the posterior fossa is suspected. It is unwise and even dangerous to do the puncture as a routine procedure at one's office or at the clinic and allow the patient to go home. The patient should be kept in bed after the puncture, flat on his back for at least 1–2 hours, and may then be permitted to have a small pillow under his head. **Quiet and repose** should be enforced. In nervous and irritable individuals, especially in tabetics with lightning pains, a dose of **codeine**, grain $\frac{1}{4}$ (0.032–0.064 gram), or **morphine sulfate**, grain $\frac{1}{4}$ – $\frac{1}{2}$ (0.008–0.016 gram), with **atropine**, grain $\frac{1}{150}$, may be given hypodermically. In very severe cases grain $\frac{1}{100}$ of **hyoscine** may be necessary. In such agitated cases it is often wise to **precede the puncture by sedative treatment**. If the patient, on a previous puncture, suffered from after effects, it is better to give an **opiate** before performing the puncture, and again after its completion. Most patients should be kept in bed for from 12–24 hours and then allowed to sit up gradually before arising. Sometimes the after-effects do not come on for 24–48 hours after puncture, in which event, if severe, **rest in bed** with an ice-cap to the head and a dose of **codeine**, is advisable. If the pain is slight a dose of **pyramidon**, 3 grains (0.195 gram), or **acetylsalicylic acid**, 5–10 grains (0.324–0.648 gram), or **acetophenetidine**, 5 grains (0.324 gram), by mouth, often suffice to control it. The writer has tried injections of pituitrin without beneficial results. If the pains persist when the patient is in the upright position, a reclining position with medication, as advised above, is indicated.

The pain usually disappears immediately when the patient lies down. The sequelæ infrequently last longer than a few days to a week, although if the patient persists in walking about, severe headache may last as long as two weeks.

During and for at least one-half hour after the removal of spinal fluid, an assistant or nurse should watch the patient carefully, especially where tumor of the brain is suspected—observing his color, pulse and respirations. A marked change in pulse or respirations, a sudden, severe headache or feeling of nausea, should immediately call for a halt in the removal of fluid, and if the pulse or respiration do not become regular and normal, or if cyanosis supervenes, **stimulation and artificial respiration** should at once be resorted to and kept up until the patient is again breathing normally.

Lumbar Puncture under Anesthesia.—In the vast majority of instances spinal puncture can be performed without the use of any anesthetic, local or general. In hypersensitive individuals **local anesthesia** may be used and a spray of **ethyl chloride** at the puncture site will usually suffice. Some operators prefer the use of **infiltration anesthesia with cocaine or other local anesthetic**. The writer prefers **novocaine** 1 per cent. for this purpose. The skin at the site of puncture is first infiltrated with a few drops of the solution, a two-inch needle of about 19–20 gauge (B & S) is then pushed through this area as far as it goes without piercing the membranes, and about 2–3 c.c. of 1 per cent. novocaine solution infiltrated, while the needle is slowly being withdrawn or as it is pushed in. After five minutes the spinal puncture can be performed painlessly. Children rarely need an anesthetic. The writer never uses it for them. In *delirium or maniacal patients* a general anesthetic may be necessary, a few whiffs of **chloroform** being given—just enough to quiet the individual. The more expert the operator, the less frequently will he resort to the use of any form of anesthesia for this procedure. Infiltration with an anesthetic has one disadvantage, in that it tends to obscure somewhat the landmarks. Under these circumstances it is wise to leave the infiltrating needle *in situ* and pass the lumbar puncture needle along it, using it as a guide or director.

After the needle is withdrawn the site of puncture is cleansed of its iodine coating with **alcohol**, dried, and a small **protective dressing** placed over the puncture hole.

Lumbar Puncture Headache.—Of the minor sequelæ of lumbar puncture, the most common as well as the most distressing to the patient is the headache which follows this procedure. It is frontal, temporal or occipital, or feels like a tight constricting band around the head, and is often throbbing and intense. If the patient persists in walking about or even in sitting up, nausea or projectile vomiting may occur. There may be faintness or weakness. Lying down promptly relieves pain and concomitant symptoms.

The cause of lumbar puncture headache is very much in doubt. It is believed that it occurs more frequently when the spinal fluid is negative than when it is positive. In other words, many believe individuals without involvement of the neuraxis, e.g., curedluetics, submitting to puncture for diagnosis are more apt to suffer than those with a definite lesion of the central nervous system. In the writer's experience this is probably not the case as patients with syphilis of the nervous system and positive spinal fluid tests suffer as much and almost as

TECHNIC OF LUMBAR PUNCTURE

frequently as normal individuals. An exception to this must be made for parietic individuals, who rarely suffer after-effects. The explanation may be in the fact that in parietics the fluid is under considerable increase of pressure, and puncture relieves this without reducing it sufficiently to bring on headache. In other individuals with marked increase of intracranial pressure, puncture promptly relieves headache due to this factor.

The headache is said to be more frequent following puncture in the sitting position or where this position is assumed within twenty-four hours after puncture; but in many patients who are kept in bed twenty-four hours after puncture the pain is not averted, though in the writer's experience it is less frequent. The amount of fluid removed is probably not a factor unless too large a quantity is withdrawn, for the removal of a few drops has been followed by a typical headache lasting a week whenever the patient assumed the upright position; and the immediate replacement of the fluid withdrawn by saline solution has had no effect in averting it. In certain cases of loss of spinal fluid through the nasal cavity or following fracture of the bone of the skull, as much as 600 c.c. has been known to be drained off within twenty-four hours without ill effect, but the patients were usually in the reclining position. This also applies to cases undergoing ventricular or cisternal puncture and following decompressive and other brain procedures where fluid is lost. According to Dana,⁶⁷ the headache is caused by irritation of the dorsal fibers of the 5th and occipital nerves when the fluid is drained away, allowing the brain to sink down on the bone. There is an acute disturbance of the mechanics of the cerebrospinal circulation. But this explanation will hardly suffice for the many instances of headache following the withdrawal of less than 5 c.c. of fluid. The explanation of MacRobert⁶⁸ is very ingenious and plausible. He points out that the pia closely invests the cord while the fluid is in the subarachnoid space between the pia and the arachnoid and dura, which are in close apposition. The latter is tough and firm and fibrous, the arachnoid, loose and full and nonvascular. The needle pierces the tough dura, makes a hole in it which may persist after the needle is withdrawn, unless the loose arachnoid plugs it up. If the arachnoid is sucked into the hole by the needle in its outward excursion, it forms a wick or funnel facilitating the seepage of cerebrospinal fluid out of the canal into the epidural space. MacRobert cites a case of headache following interruption of a puncture after the needle had entered the dural sac but before any fluid was withdrawn. The constant leakage into the epidural space causes the cushion of fluid at the base of the brain to be lost and when the patient sits up the entire weight of the brain is impacted through the pons to the basilar plexus of veins on the clivus of the occipital bone. The veins are soft and compressible in contradistinction to the sinuses in the skull, which are tough and not readily compressible. The venous flow is impeded in its passage through the compressed vessels and is forced to travel by other crowded pathways, with a rise of venous pressure and a coincidental rise in intracranial pressure. When the patient lies down the weight is lifted off these vessels, circulation is restored and the headache is relieved. The healing of the small hole in the dura in a few days or a week allows the fluid to reaccumulate, restores the water cushion at the base of the brain, and so adjusts the mechanism of the cerebrospinal pressure and circulation as to remove the cause of

the lumbar puncture headache. This suggests the use of a fine needle with a short bevel but sharp point, which will make as small and fine a hole as possible, in order to prevent fluid seepage into the epidural space.

TECHNIC OF CISTERNAL PUNCTURE

This procedure was first described by Wegeforth, Ayer and Essick¹⁵⁵ in 1920 and by Eskuchen¹⁵⁷ in 1923. Ayer¹⁵⁶ in 1923 described his method of puncture of the cisterna magna. Since this time numerous articles have appeared in the literature. For the details of the technic the reader is referred to the articles of Ayer and of Eskuchen as well as to a recent paper by Spiegel,¹⁵⁸ who has adopted the Eskuchen technic and invented a simple and safe needle for this operation.

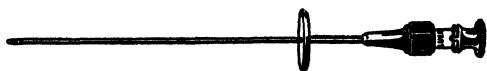


FIG. 12.—NEEDLE, 19 gauge steel made in two lengths, six and eight cm. Guard placed at the end of needle proper. (Spiegel)

The writer has used both the method of Ayer and of Spiegel and prefers the latter. The patient should be kept in the reclining position and the same precautions as to asepsis and watchfulness for respiratory changes should be observed as described under lumbar puncture technic. The following diagrams illustrate the direction of the needle in puncturing the patients as well as the fundamental differences in the Ayer and Eskuchen techniques.

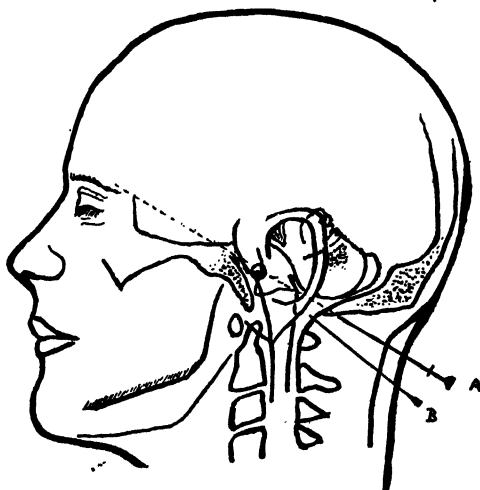


FIG. 13.—COPY OF TRACING FROM FROZEN SECTION OF HEAD CUT IN MIDSAGITTAL PLANE, from original article of Dr. James B. Ayer, Puncture of the Cisterna Magna. A, Eskuchen needle at point of orientation. B, Needle *in situ*. (Spiegel)

It seems, according to the opinion of most contributors to the literature on the subject, that in expert hands and with due precautions, cisternal puncture is, not hazardous to life; indeed, most observers believe it to be just as safe as lumbar puncture. In most instances it is a painless procedure and has the advantage of avoiding the headaches which so frequently follow lumbar puncture. As a rule, the puncture can be done in the clinic or office and the patient is able to go about his business soon thereafter. Of course where tumor cerebri is suspected, the patient should be kept in bed after the puncture.

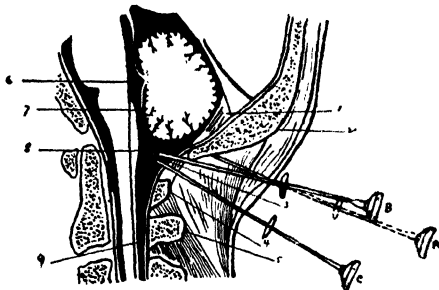


FIG. 14.—1, Fossa for cerebellum; 2, occipital protuberance; 3, postoccipital atlantal ligament; 4, transverse process of atlas; 5, spinous process of axis; 6, fourth ventricle; 7, foramen magnum; 8, cisterna magna; 9, subarachnoid space. A, needle at point of orientation; B, needle point depressed and in cisterna; C, Ayer direct method needle within cisterna. (Spiegel)

It seems to the writer that cisternal puncture will have an increasingly wider field of usefulness as experience shows its safety. For routine diagnosis in syphilis of the central nervous system, in the diagnosis of spinal cord tumor either with or without the injection of lipiodol, together with manometric readings at the cisternal and lumbar levels and in cases of spinal block from inflammatory adhesions, the method offers many advantages. It should not be undertaken without adequate preliminary training on the cadaver.

METHODS OF EXAMINATION OF THE CEREBROSPINAL FLUID

The number and kind of examinations to which a specimen of cerebrospinal fluid should be subjected will, of course, depend upon the suspected clinical diagnosis. For example, in an acute condition of primary or secondary origin with symptoms of meningitis, it will be of diagnostic importance to determine the physical character of the fluid and its cellular and bacteriological content, with less necessity for the determination of the various biological reactions. On the other hand, in a chronic condition with involvement of the central nervous system, the bacteriological studies will be of little or no significance, while the Wassermann, colloidal gold tests, cytological and globulin tests will be of paramount importance. It is only in exceptional circumstances that a complete examination of cerebrospinal fluid is necessary.

The great degree of importance attached to the outcome of the various tests of the cerebrospinal fluid about to be mentioned, not only in

the diagnosis but also in the prognosis of many diseases, imposes upon the examiner an equally grave burden of responsibility which can be fulfilled only by sufficient experience in carrying out the technical details of the various examinations and by conscientiousness and accuracy of observation in reading and recording the results. The relatively great rôle which laboratory diagnosis is playing in relation to clinical diagnosis—especially as regards diseases of the central nervous system—and the increasing favor with which clinicians are looking upon laboratory examinations, bespeak an enviable degree of confidence on the part of the practitioner for the pronouncements of the laboratory worker.

It cannot be too often iterated, however, that the facts revealed by pathological examination must always be considered in relation to the clinical condition of the patient and the data ascertained by a thorough physical examination. Any one fact or group of facts revealed by examination of the blood or cerebrospinal fluid cannot be said always to outweigh the sum of facts obtained by a consideration of the entire clinical picture. It is only in relating laboratory data to subjective and objective findings and their proper balancing that the true composite picture of disease is completed and the patient's interests conserved. This is true not only in the use of laboratory data in diagnosis but equally, if not more so, in the prognosis of syphilitic diseases of the central nervous system, which will be considered under a separate heading.

A consideration of the above facts indicates the necessity for a greater degree of coöperation on the part of the clinician and of the laboratory worker, so that the data as revealed in the laboratory may be appreciated in their proper perspective. Under a separate heading we have enumerated the character of the cerebrospinal fluid in health and disease and we will now proceed to a consideration of the technic of the various laboratory tests and their significance.

It is important that determinations are carried out as soon after withdrawal of the fluid as possible and that the fluid is carefully stoppered, to avoid contamination and evaporation, and that the test tubes are carefully prepared to insure sterility and to avoid chemical changes as a result of too acid or too alkaline reaction from improperly cleansed tubes.

Tests for Protein (Globulin and Albumin).—The test for protein was popularized by Nonne⁶⁹ in the diagnosis of syphilis of the nervous system. The principal protein constituents of the cerebrospinal fluid are globulins (euglobulin, pseudoglobulin, fibrinoglobulin) and as a rule our tests are confined to their detection alone. As blood gives the reaction, fluids must be blood-free if the test is to be of any value. Even traces of blood vitiate the results. Centrifugalization removes the cells but leaves blood serum behind.

Total Protein.—*Total Protein Determination.*—In recent years it has become necessary to determine accurately the total protein content of the cerebrospinal fluid, especially when puncture is done at various levels and for comparison of the lumbar and cistern protein contents. Thus a differential point of great significance in diagnosis between lesions at various levels is afforded. Most of the tests depend upon the precipitation of the protein by means of picric or sulfosalicylic acid or by boiling with trichloroacetic or other acid.

Aufrecht's Albuminometer.—This is a conical tube designed to fit the centrifuge. The fluid is filled to the level U in the tube and then to the

mark R, with a solution of picric acid, 1.5 grams, citric acid, 3 grams and distilled water, 100 c.c. After inverting several times, it is centrifuged for 5 minutes at 2,000 to 3,000 revolutions per minute. The level of the precipitate is then read off on the markings on the tube, and represents the percentage of protein in 4 c.c. of fluid.

*Method of Delis and Ayer.*¹⁸—This method depends upon precipitation by sulfosalicylic acid and comparison with a standard made by precipitation of a protein solution of known strength, using a colorimeter or nephelometer. For the test, 0.6 c.c. spinal fluid, 0.4 c.c. distilled water and 1 c.c. of a 5 per cent. sulfosalicylic acid solution are added to a test-tube, mixed by inverting several times and allowed to stand for 5 minutes. It is then placed in a colorimeter and read against a suitable standard, made as follows: 200 c.c. of fresh human serum, clear and uncontaminated, are diluted with 200 c.c. of a 15 per cent. sodium chloride solution, filtered, and the protein percentage determined by the Kjeldahl method. A few c.c. of chloroform are added as a preservative, and it is kept tightly stoppered in the ice-box. It keeps two or three months. For use, two diluted standards containing 20 and 30 mg. of protein per 100 c.c. are made. For the test, the standard suspension is made by adding 3 c.c. of the 0.02 or 0.03 per cent. protein with 3 c.c. of the 5 per cent. sulfosalicylic acid solution.

*Method of Mestrezat.*²⁰—To 2 c.c. of cerebrospinal fluid, add 0.3 c.c. of 30 per cent. trichloroacetic acid. Boil rapidly. Set aside for 20 minutes to cool. Then shake and compare with standard scale of Mestrezat.

GLOBULIN REACTION.—1. *Noguchi's*⁷⁰ *Butyric Acid Method for Globulin.*—The writer prefers this method, which is simple, sensitive and reliable. The only disadvantage is the pungent and unpleasant odor of the butyric acid ingredient.

Add to 0.2 c.c. spinal fluid 0.5 c.c. 10 per cent. butyric acid in normal salt solution (0.9 per cent.)

Heat gently and add 0.2 c.c. normal sodium hydroxide.

Boil about $\frac{1}{4}$ minute and allow to stand about 5–10 minutes.

Slight flocculation and turbidity are read as one plus (+).

Heavy flocculation and turbidity are read as two plus (++).

Normal fluids give a faint uniform opalescence. Any degree of fine flocculation is a positive reaction.

2. *Nonne and Apelt*⁷¹ *Phase I Reaction.*—Add equal parts of spinal fluid (say 0.5 c.c.) and saturated solution of chemically pure ammonium sulfate. Allow mixture to stand, after shaking, for about 3–5 minutes. A positive reaction is indicated by a marked turbidity or precipitation. Normal fluids give a faint opalescence or remain clear.

3. *Ross-Jones Modification.*⁷²—This consists in layering the spinal fluid over the saturated solution of ammonium sulfate. A white ring indicates a globulin increase.

4. *Method of Pandey.*⁷³—Add 1 drop of cerebrospinal fluid carefully to saturated, watery solution of carbolic acid. A bluish-white ring indicates abnormality, while a whitish ring indicates a stronger reaction. The degree of reaction can be graded as one or two or more plus, by experience.

5. *Method of Kaplan.*⁷⁴—Heat 0.5 c.c. of spinal fluid in a small (8×1 c.c.) test tube to the boiling point twice, and add 3 drops of 5 per

cent. butyric acid in normal salt solution, and then 0.5 c.c. of a supersaturated ammonium sulfate solution. The latter solution is allowed to flow gently down the side and under the contents of the test tube. Set aside for about 20 minutes. An excess of globulin is indicated by a thick granular ring. The reaction can be made a quantitative one by adding graduated amounts of spinal fluid—from 0.1–0.5 c.c. in 5 tubes—adding salt solution to bring the total amount up to 0.5 c.c. and then proceeding with the test, as indicated.

6. *Method of Amoss*.⁷⁵—A suitable reagent for the globulin test in spinal fluid may be prepared by dissolving 3 grams of anhydrous potassium dihydrogen phosphate in 100 c.c. of distilled water and adding 0.05 c.c. of glacial acetic acid. In making the test, 0.2 c.c. of the spinal fluid and 0.6 c.c. of the reagent are mixed in a small agglutination tube and placed in boiling water for six minutes. This test is slightly less delicate than the Noguchi test, but offers some advantages over the latter for field work.

Tests for Albumoses.—1. *Method of Kafka*.—2 c.c. of cerebrospinal fluid are dialyzed against 10 c.c. of distilled water for 16 hours, at 30° C., using a dialyzing thimble (Schleicher and Schull) impervious to albumen. Then add 0.2 c.c. of a 1 per cent. ninhydrin solution to the dialysate. Boil for one minute and allow to stand one-half hour. A gray-blue, blue or violet color indicates the presence of a positive ninhydrin reaction, which speaks for acute meningitis.

2. *Method of Sicard*.—Boil 5 to 6 c.c. of spinal fluid after saturating with Na_2SO_4 or NaCl , to coagulate proteids. Filter several times and add to the filtrate, crystals of NH_4Cl from a supersaturated watery solution. If albumoses are present an opalescence appears around the crystals, which disappears partly on heating, to re-appear on cooling.

Potassium Permanganate Reduction Test.—This is a test devised by Mayerhofer⁷⁶ for the detection of organic substances in the spinal fluid. Normal spinal fluid reduces potassium permanganate when boiled in an acid medium and the amount of decinormal potassium permanganate solution which, boiled for 10 minutes in a strongly acid medium, is reduced by 1 c.c. of cerebrospinal fluid, is called the permanganate reduction index. Normal fluids usually give an index around 2.0–2.3 c.c. Fluids containing larger amounts of organic matter, the result usually of inflammation in the membranes, give higher indices—up to and above 2.5.

Hoffman and Schwartz⁷⁷ classified the indices into 3 groups, as follows:

- Low indices—below 2;
- Borderline indices—between 2 and 2.5;
- High indices—over 2.5.

They found that all normal fluids or fluids from patients not presenting inflammatory lesions of the brain or meninges give low indices. Brain tumors give a low index. The early stages of inflammatory processes give borderline indices, as do also serous meningitis, encephalitis or hyperemia of the brain. High indices indicate inflammation of the cerebrospinal tissue or the membranes. It was thought that the test was of specific corroborative value in the differential diagnosis of tuberculous meningitis and poliomyelitis, but this is probably not the case, although the test is of some value in the determination of an inflammatory change in the central nervous system. The other protein

tests are probably of as much value and have the advantage of simplicity.

This test is performed as follows: First determine how much N/10 oxalic acid is necessary to reduce completely 10 c.c. of N/10 potassium permanganate in the presence of sulfuric acid, as follows:

- 10 c.c. N/10 potassium permanganate;
- 10 c.c. sulfuric acid dilution (1:3 H₂O);
- 50 c.c. distilled water.

Then perform the test in the following manner:

- 1 c.c. cerebrospinal fluid;
- 10 c.c. diluted sulfuric acid;
- 50 c.c. distilled water.
- Boil gently for 10 minutes and add
- 10 c.c. N/10 potassium permanganate.
- Then add amount of oxalic acid determined above.
- Again add N/10 potash permanganate from buret until faint pink color appears.

The reading in cubic centimeters gives the reduction index. The modification of Boveri⁷⁸ is performed with 1 c.c. of spinal fluid, blood free, and 1 c.c. of potassium permanganate (0.1-1000 c.c.). The fluid from undoubted cases of meningitis of various types turns this solution a bright yellow immediately. Fluids from mild cases of meningeal irritation take from 2-3 minutes to decolorize. Rubenstone⁷⁹ found the test not of specific but of corroborative value in differentiating between normal and abnormal fluids.

Tests for Chlorides.—Chlorides are precipitated as insoluble silver chloride, using as an indicator potassium chromate, forming red silver chromate.

To make silver solution, dissolve 5.814 grams of pure AgNO₃ in a litre of distilled water. Keep the solution in a dark bottle. In the test, mix 2 c.c. of spinal fluid with 15 c.c. of distilled water. Add one drop 10 per cent. potassium chromate solution. Run the silver nitrate solution from a buret stirring constantly. The end point is reached when the color changes to orange-yellow. Each c.c. of solution used indicates one gram of chloride per 1,000 c.c. or 100 mg. per 100 c.c.

Lactic Acid Test.—Add to 6 drops of a standardized Fehmann's reagent (5 per cent. FeCl₃—1 part; 1 per cent. phenol—5 parts) spinal fluid, drop by drop, until the color changes to yellow.

- 1 to 3 drops indicate a marked reaction ++
- 3 to 6 drops indicate a moderate reaction +
- 6 to 10 drops indicate a weak reaction ±

Tests for Reducing Substance (Glucose).—The ordinary Fehling's reagent is used in this test. A drop or two of Fehling's copper solution and of Fehling's alkaline solution and a few drops of water are first heated to boiling point, to determine the freedom of the reagent from reducing substance. Then an equal amount of the cerebrospinal fluid to be tested is added. If small quantities of reagent are used, no more than 0.5 c.c. of spinal fluid is required for the test. The presence of sugar is indicated by the red brick-dust precipitate of cupric oxide.

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Instead of Fehling's solution, Benedict's sugar reagent may be used. The sugar test is of corroborative value only. Its significance has been considered in detail elsewhere.

Test for Other Constituents.—Acetone, diacetic and oxybutyric acid may appear in the cerebrospinal fluid under the same conditions, causing the appearance of these substances in the blood and the urine, and may be of diagnostic value in obscure cases of coma. The tests are applied similarly to those for the detection of these bodies in other fluids.

Cytological Examination of the Cerebrospinal Fluid.—Under normal conditions the cerebrospinal fluid contains very few cellular elements—a few small lymphocytes which, when viewed under the microscope, have a very small amount of protoplasm encircling the comparatively large, round or oval nucleus, an occasional large lymphocyte and rarely an endothelial cell, usually with an irregular or tailed body. With exact quantitative methods of examination of the cellular content of the fluid, by means of the Fuchs-Rosenthal or Thoma-Zeiss chamber, the normal range of cells is variously estimated as from one or two up to eight or ten. In the writer's experience any number greater than five, six or seven should be looked upon with suspicion, while ten cells or over are to be considered pathological. The novice in examination of the cerebrospinal fluid should learn to differentiate between lymphocytes present in puncture fluid and red blood cells which may be present even in apparently absolutely clear specimens. For the purpose of aiding in differentiation a diluting fluid containing acetic acid and the high power objective of the microscope should be used.

There are two methods of cytological examination of the cerebrospinal fluid. The first is that of the French and was outlined by the pioneers in the field of cytological diagnosis, Sicard⁸⁰ and Widal, Sicard and Ravaut,⁸¹ and Ravaut.⁸² The fluid is centrifuged, the cells thrown down and the sediment examined under the microscope. In this way it can be determined by experience whether the cells are increased, and to what extent. This method is obviously inferior for quantitative readings to the more exact one of spreading out a definite quantity of fluid on a ruled platform, using either a specially designed chamber, the Fuchs-Rosenthal chamber or the ordinary blood-counting chamber of Thoma-Zeiss.

In speaking of cytological counts throughout this article, the writer refers to the number of cells to each cubic millimeter as determined by the use of the Fuchs-Rosenthal chamber. This is a ruled platform 16 mm. square and 0.2 mm. deep, ruled into 16 large squares, each subdivided into 16 smaller squares and holds 3.2 c. mm. of fluid between the ruled platform and the superimposed cover-slip. The spinal fluid should be examined as soon after withdrawal as possible. In the writer's laboratory it is a practice to examine fluids within an hour or two after puncture. If allowed to stand, the fluid should be thoroughly shaken before counting the cells. The fluid should be free from blood, and for this purpose the collection at the time of the puncture should be made into two or three tubes, so that if there is a small amount of blood in the first, the last tube may be clear. If definitely bloody, however, the fluid is not suitable for cytological examination.

The following diluting fluid is of value in bringing out more clearly the nuclei of lymphocytes and taking the occasional erythrocyte present in the cerebrospinal fluid:

Methyl violet, 1.0 gram;
Glacial acetic acid, 2.5 c.c.;
Distilled water, 100.0 c.c.

This is drawn up to the 1.0 mark in an ordinary white blood-cell pipet and the fluid for examination is then sucked up to the 11 mark, thoroughly shaken, a few drops expelled, and a drop placed on the cell-counting chamber platform and the cover-glass slid over into place. All the lymphocytes are counted within the outside triple-ruled line, i.e., the entire ruled field. To obtain the number of cells in a cubic millimeter, multiply the number of cells counted by 11 and divided by 32. If the Thoma-Zeiss chamber is used, the entire field of 400 small squares is counted and the result multiplied by 100 and divided by 11. On account of the small size of the field, the use of this chamber is not nearly as satisfactory as the preceding one.

In order to determine the relative percentage of various cells in the cerebrospinal fluid, a small amount is centrifuged, a drop of the sediment spread out on a glass slide, dried in the air, fixed with methyl or absolute alcohol and stained with Giemsa or Wright stain or with methyl green-pyronine solution (3 parts methyl green saturated solution, 1.1 parts of pyronine saturated solution). The cells are then differentiated under oil immersion power.

For a more careful examination of the morphology of the cells of the fluid and especially for the determination of plasma cells, the following method, adopted from Alzheimer,⁸³ is of service:

About 10 c.c. of fluid are collected in 5 c.c. of 95 per cent. alcohol and centrifuged for one hour. The alcohol is poured off and replaced by absolute alcohol for 30 minutes, ether alcohol 30 minutes and ether 30 minutes. This is then embedded in celloidin and cut, then stained with Unna-Pappenheim for a few minutes, and gently warmed until fluid steams. Finally, it is treated with water, 95 per cent. alcohol, and embedded in balsam.

The various types of cells can thus be differentiated. Plasma cells are somewhat larger than lymphocytes; the nuclei stain intensely and the chromatin markings are also intense. The protoplasm of the cell is finely granular and reddish. These cells are found more frequently and in large numbers in dementia paralytica but have also been demonstrated in acute inflammatory lesions of the membranes and in syphilis of the brain and cord other than general paresis. In connection with the early diagnosis of general paresis and its differentiation from other similar clinical conditions, further light on the significance and relative frequency of plasma-cells in the fluid is desirable.

SIGNIFICANCE OF PLEOCYTOSIS.—In *inflammatory lesions of the membranes* the number of cells present in the fluid is increased (pleocytosis—Nonne), and the degree of increase is in proportion to the intensity of the inflammation. In pyogenic inflammations, as in the various meningitides or in abscess of the brain which has ruptured in the vicinity of the ventricles or subarachnoid space, the fluid may be frankly turbid, while in milder types of inflammation the cells may be only moderately increased with a clear or slightly turbid fluid, as in cases of tuberculous meningitis, poliomyelitis and certain syphilitic nervous manifestations. As a rule, in intense inflammatory lesions and at times in the beginning of certain conditions where the meningeal response is milder—like

tuberculous meningitis and poliomyelitis—the polynuclears predominate, while in the less intense inflammations of the meninges and the more chronic lesions of the membranes, including the various syphilitic diseases of the central nervous system, the lymphocytic varieties predominate as they do also after the first week or so in acute poliomyelitis. *Irritative lesions of the membranes* give rise to the appearance of lymphocytes in the fluid in proportion, as a rule, to the intensity of the meningeal insult, though rarely to the degree manifested in the true exudative processes. Occasionally pleocytosis may occur in sympathy with lesions contiguous to the membranes without actual inflammation in the coverings of the brain and cord. This type of meningitis sympathica has been considered in detail under a separate heading. In *herpes zoster* the lymphocytes are increased in number, often 50 or more to the cubic millimeter being found. As a rule, the pleocytosis runs hand in hand with the increase of globulin (phase 1), though there are a number of exceptions which are best considered under the various cerebral and spinal diseases, to be briefly discussed later.

Bacteriological Examination of the Cerebrospinal Fluid.—It is of the utmost importance to the clinician to have, at the earliest possible moment following the appearance of symptoms suspicious of an infection of the meninges, an accurate examination of the cerebrospinal fluid to determine, first, whether infection exists and, second, the type of organism responsible for the infection. In view of the efficacy of intraspinal injections of antimeningococcus serum, the puncture should be done early and the clinician should be prepared to administer the serum at the same time. If the fluid is turbid, spreads may be made at once and the meningococcus looked for at the bedside, or, at any rate, where a strong suspicion exists of the presence of a meningococcus meningitis, the serum should be administered pending the outcome of the tests.

For the details of *technic of bacteriological examination of the cerebrospinal fluid*, the reader is referred to appropriate works on the subject. Suffice it to mention that where an inflammatory lesion of the meninges is suspected and if a bacteriological study of the fluid is to be carried out, especially if spreads of the sediment prove negative for bacteria, the puncture must be done under the strictest rules of asepsis and the fluid obtained in sterile test tubes. In the first of two or three test tubes one or one and one-half c.c. of fluid are gathered for inoculation on the appropriate culture media; for spreads to determine the presence of bacteria by use of the Gram stain; for staining for tubercle bacilli, especially if the latter test proves negative; and for sugar tests. In the second test tube 2–3 c.c. are obtained for quantitative cytological and differential count and for the Wassermann test and colloidal gold test. Into a third test tube 1–2 c.c. may be taken, especially if the first two contain even the slightest trace of blood and to provide for a surplus in case of repetition or accident to one of the other tubes or for animal inoculation.

The following organisms have been found in cerebrospinal fluid either as primary invaders of the meninges or secondary infections from a primary focus elsewhere in the body—*Diplococcus intracellularis meningitidis*, tubercle bacillus, pneumococcus, Friedländer's bacillus, influenza bacillus, streptococcus, *Staphylococcus albus* and *aureus*, and colon bacillus. *Treponema pallidum* has been found in the cerebrospinal fluid by means of the dark field microscope, cultures and inoculations into rab-

bits' testes by Noguchi,⁸⁴ Nichols and Hough⁸⁵ and others. Trypanosomes have been described by Bruce⁸⁶ and by Castellani,⁸⁷ *Cysticercus cellulosæ* by Hartman,⁸⁸ actinomyces by Sicard⁸⁹ and trichinæ by Van Cott and Lintz.⁹⁰ Organisms have also been found in typhoid and typhus fevers, plague, anthrax, blastomycosis and Malta fever.

EXAMINATION OF THE CEREBROSPINAL FLUID FOR TUBERCLE BACILLI.—A somewhat larger quantity of fluid should be taken for examination for tubercle bacilli, say 5–10 c.c. The fluid is usually clear, and on standing a few hours a fine fibrin net usually appears. The fluid is centrifuged at highest speed in a conical centrifuge tube for at least 15 minutes—better, 30 minutes—and all but two or three drops of the fluid decanted off. These last few drops are placed on a slide, together with the fibrin net. The slide or cover-slip containing the sediment is placed in an incubator at 37° C. until dried and then stained for tubercle bacilli as follows:

Fix by passing through flame quickly three times.

Add carbol fuchsin and heat gently until steaming for 5 minutes.

Pour off stain and decolorize with 20 per cent. HNO₃ for 5 minutes.

Wash with alcohol until clear. Wash with tap water.

Counter-stain with 1 per cent. aqueous solution methylene blue.

A careful and prolonged search is usually necessary to detect the organisms. A specimen should not be called negative until the slide has been examined for at least 2–3 hours. By this technic, Bernstein⁹⁰ has been able to detect tubercle bacilli in more than 95 per cent. of his cases.

Serology of the Cerebrospinal Fluid.—**THE WASSERMANN REACTION.**—The most important serological examination to which the spinal fluid is subjected is the Wassermann test. The details of the technic of this procedure cannot be given here on account of lack of space, and for them the reader is referred to special works on the subject. The reaction is carried out in a similar manner and with all the necessary controls and safeguards utilized in the Wassermann test of the blood, with the following exceptions: The spinal fluid is used without inactivation and in larger amounts than can be utilized for examination of the blood without interfering with the specificity of the reaction. In routine spinal fluid Wassermann examinations the fluid is tested in amounts ranging from 0.1 c.c. to 1.0 c.c. (modification of Hauptmann and Hoesli⁹¹), being a distinct improvement over the original technic of Wassermann⁹² and of Plaut,⁹³ who introduced the reaction in 1906 and used 0.2 c.c. as a maximum quantity. The spinal fluid under ordinary conditions is rarely possessed of anticomplementary or auto-inhibitory factors, and the use of 1.0 or even 2.0 c.c. as a maximum—as is the practice of certain serologists—results in clear-cut reactions. Indeed, owing to these factors, the results of the spinal fluid Wassermann test are rarely “suspicious” or “inconclusive,” but can be read in terms of complete or partial inhibition in any quantity from 0.1 to 1 c.c. used in the test. The writer in routine cases uses five tubes, the amounts of spinal fluid ranging from 0.05 to 0.5 c.c., and since all the proportions of the regular Wassermann system are reduced by half in his method, the readings are equivalent to 0.1 to 1 c.c. in the regular system.

SPECIFICITY OF THE WASSERMANN REACTION IN THE CEREBROSPINAL FLUID.—It is beyond the scope of this article to go into a consideration of the specificity of the Wassermann reaction. Suffice it to say that for all practical purposes and with the exception of diseases of the tuberculous variety, like leprosy, and of frambesia (yaws), easily distinguishable here from syphilis on clinical grounds, the presence of a positive Wassermann reaction in the spinal fluid means syphilis of the nervous system. On theoretical grounds it is possible to assume that under certain conditions, possibly in early syphilis more particularly, coincident with the general spread of the virus, there is an alteration of the histologic structure of the choroid gland, permitting the passage into the cerebrospinal fluid of the so-called syphilitic antibody or reacting substance from the blood without an actual lesion referable to the nervous tissue. But it seems more likely in these circumstances—especially in view of the prevalence in as high as 80 per cent. of these cases of a pleocytosis and globulin increase—that we are dealing with an active syphilitic involvement of the neuraxis or only of its membranes with the appearance of the positive reaction in the fluid. The fact that certain cases with positive reactions showed no anatomical change on autopsy is not conclusive evidence of the absence of the disease. A small focus of disease sufficient to give a positive reaction might easily be overlooked on gross postmortem examination and even after a cursory microscopic study. The appearance of definite clinical manifestations of involvement of the nervous system in so many cases of primary and secondary lues makes this view the more likely one.

Recently in a case of early secondary lues with the chancre still present, the writer found all the reactions in the spinal fluid, including the Wassermann reaction in 0.1 c.c. positive, and clinical examination revealed involvement of the optic and the acoustic nerves. And so it seems advisable from a practical standpoint to look upon the positive Wassermann in the spinal fluid as an evidence of involvement of the nervous system, especially if the fluid is positive even in the smallest quantity (0.1 c.c.) used in the test. It follows as a matter of course that in cases where there is a definite involvement of the central nervous system, "antibody" formation occurs there with the appearance of the bodies in the fluid causing a fixation of complement and a positive Wassermann reaction, and very possibly there is also an augmentation by filtration through the choroid plexus. The possibility exists, where a positive reaction is found when using only 1 or 2 c.c. of fluid, which disappears soon after lumbar puncture or intraspinal therapy, that the reaction may be due to secretion by the choroid plexus of reagin from the blood with the appearance of a positive reaction. This is rather improbable, however, in view of the physiological facts stated earlier in the article which tend to show that the spinal fluid is rapidly secreted and may be re-absorbed back into the blood within, say, three hours. The subject will be discussed further under syphilis of the nervous system.

HEMOLYSIN REACTION—HEMOLYTIC ANTIBODIES.—In a consideration of the physiology of the cerebrospinal fluid, it was pointed out that under normal conditions the choroid plexus is impermeable to a variety of immune substances, but that, under certain conditions existing in disease, antibodies make their way past the barrier of the plexus and appear in the fluid. Attempts have been made to utilize this phenomenon

in differential diagnosis. For example, hemolytic antibodies are present in the fluid in 85 per cent. of general paretics but they also appear with almost equal frequency in marked inflammatory lesions of the membrane in other conditions. Weil and Kafka⁹⁴ describe a test for the detection of this hemolysin. Its presence, in the absence of active inflammation of the meninges, is suggestive of general paresis, but, on the whole, the test has not proved of much value in diagnosis.

COMPLEMENT-FIXING BODIES, ETC.—Complements, precipitins and agglutinins may also appear in the fluid in certain disease conditions, but their detection is not of clinical value.

PRECIPITIN REACTION OF VINCENT AND BELLOT.—Vincent and Bellot⁹⁵ described a test for the detection of the antigenic substances or precipitin in the cerebrospinal fluid of patients with epidemic cerebrospinal meningitis. To the spinal fluid a few drops of antimeningococcus serum are added and the mixture incubated for a few hours. After allowing the tubes to stand for 8–15 hours, a precipitate indicates the presence in the fluid of precipitating substance for meningococci and is proof of the presence of meningococcus meningitis. Together with Heiman, the author made some studies along these lines, with inconclusive results.

BRUCK'S NITRIC ACID REACTION IN SYPHILIS.—Bruck,¹³³ in 1917, described a test based on the observation that the precipitate in the serum of a syphilitic individual, after the addition of nitric acid, does not dissolve as readily as the precipitate formed in the serum of a non-syphilitic. In 200 tests Bruck got similar results with this reaction to those obtained with the Wassermann test. Three tests positive with the Wassermann reaction gave negative Bruck's tests, while 2 negative Wassermann tests were positive with the nitric acid test. Of 200 non-syphilitic sera all but 4 were negative, and those 4 were from febrile cases.

Stillians,¹³⁴ in 209 cases, found that in more than 25 per cent. of the cases the test disagreed with the Wassermann reaction and that in 24 per cent. the reaction was nonspecific. In 100 cases Toyama and Kolmer¹³⁵ found that both tests agreed in 70 per cent., being positive in 62 per cent. and negative in 8 per cent. In 23 sera the Wassermann reaction was negative, the Bruck test positive. Eight of these were negative for syphilis clinically and gave no history of the disease. Thus the reaction was nonspecific in 8 per cent. of the cases. Of 15 cases with a negative Wassermann reaction but frankly specific (15 per cent.), the Bruck test was positive. Of 6 frankly positive specific sera in which the Wassermann reaction was positive, the Bruck test was negative. Toyama and Kolmer applied this test to the spinal fluid for the first time. Thus it seems that the test is—on account of the large percentage of nonspecific results—of doubtful value as a diagnostic test, although further work is necessary, especially in the testing of non-specific sera, to define its actual worth.

Technic.—Only clear serum can be used. Opalescent or turbid sera cannot be used.

Add 0.5 c.c. serum to 2 c.c. distilled water (or 2 c.c. spinal fluid).

Mix gently to avoid frothing. Add 0.3 c.c. 25 per cent. dilution of chemically pure nitric acid (100 c.c. HNO_3 + 225 c.c. distilled H_2O). Mix gently and stand aside at room tempera-

ture for exactly 10 minutes. While adding the acid the tube should be gently shaken to avoid a precipitate in normal serum. The exact time limit must be carried out.

To the white precipitate add 1.6 c.c. distilled water, putting the finger over the tube, and invert gently a few times, but prevent frothing. Wait ten minutes and again invert 3 times. Read result after allowing test to stand at room temperature for 30 minutes.

With normal serum the precipitate is supposed to dissolve completely or there may be faint opalescence, but with syphilitic sera small flakes appear which do not dissolve.

Colloidal Gold Test.—This test is based on the experiments of Zsigmondy⁹⁶ in the use of solutions of colloidal gold for protein estimation. Lange⁹⁷ applied the method to the cerebrospinal fluid and found that, contrary to the results of Zsigmondy (who found that proteins protected colloidal solutions up to a certain point), the proteins of the spinal fluid, especially in general paresis, tabes and other syphilitic conditions, precipitated the colloidal gold.

Solutions of colloidal gold are very sensitive to the coagulating action of electrolytes. There is a physicochemical reaction in which the electrolyte becomes dissociated into positive and negative ions; there is interaction with the finely dispersed colloidal particles which usually carry a negative charge with the formation of neutral aggregates. Conditions are then favorable for the action of the precipitating forces of surface tension. Ultimately precipitation occurs when the aggregates become large enough to fill the bottom of the tube, and complete decolorization occurs.

Lange found that normal spinal fluids diluted with 0.4 per cent. sodium chloride solution caused no change in properly prepared solutions of colloidal gold. Abnormal fluids containing a large protein content cause either partial or complete precipitation of colloidal gold solution with resulting color changes, occurring in curves more or less specific for certain diseases, especially syphilis. However, the exact nature of the test is still unknown. Lange looked upon various reactions as indicating different protein mixtures, and Zaloziecki⁹⁸ thought the colloidal gold test was an immunity reaction, while others look upon it as a purely physical phenomenon in the nature of an electrical reaction. Eskuchen⁹⁹ believes that the colloidal gold reaction is of value even when all other spinal fluid tests are negative and suggests the term "5th reaction" (in addition to Nonne's four reactions) for it. He believes it is more sensitive and specific than any of these. This seems to be the opinion of many laboratory workers, which the writer cannot subscribe to at present, but it is agreed that, owing to the great difficulty of preparing the reagent, the test has not had the wide application that this favorable opinion warrants. Undoubtedly the great need is for a standard, invariable and simple method of preparation, for beyond this the test offers little difficulty in its performance.

Methods of preparation are numerous, and at times good solutions are obtained with all of them, and then again all are equally unsatisfactory. In the various details of preparation of colloidal gold the reader is referred to the work of Miller and Levy,¹⁰⁰ Miller, Brush, Hammers and Felton¹⁰¹ and Black, Rosenberg and McBride.¹⁰²

The writer has recently been successful with the following technic:

For every 100 c.c. of triply distilled water add 1 c.c. of a 1 per cent. solution of gold chloride and 0.7 c.c. of a 2 per cent. solution of sodium carbonate. These may be added at low temperature and the mixture may then be heated rapidly with a triple Bunsen burner to 90° C. At this point 1 c.c. of a 1 per cent. solution of formaldehyde should be added, while stirring vigorously with the thermometer. If the first signs of change in the colorless fluid do not appear in a few minutes, formaldehyde, drop by drop, may be added until reduction occurs, stopping the addition of formaldehyde the moment the reddish color begins to appear. If the color does not become a deep salmon red, a few drops more of formaldehyde may be added while the solution is boiling. It is essential before performing the test to be sure that the solution of colloidal gold fulfills all the conditions imposed by Miller and Levy, viz.:

1. The solution must be transparent and of brilliant red-orange or salmon-red color.
2. 5 c.c. must be completely precipitated by 1.7 c.c. of 1 per cent. solution of sodium chloride within one hour.
3. The solution must be neutral in reaction on the day used.
4. The solution must give a typical curve with a paretic fluid.
5. The solution must give more than a No. 1 reaction with a normal fluid.

The test is carried out as follows:

Eleven test tubes are placed in a row in a test tube rack.

Into the first put 1.8 c.c. of a 0.4 per cent. sodium chloride solution freshly prepared.

Into the other ten put 1 c.c. of a 0.4 per cent. solution chloride solution freshly prepared.

Into the first tube put 0.2 c.c. blood-free, clear spinal fluid to be tested.

From the first tube, after mixing thoroughly, transfer 1 c.c. to the second tube. Mix and transfer from this second tube 1 c.c. to the third.

Proceed up to the tenth tube. Discard the 1 c.c., instead of adding it to the 11th tube, which is the control, and to which no spinal fluid is added. This gives a dilution of spinal fluid of 1: 10 in the first tube; 1: 20 in the second; and so on up to 1: 5120 for the 10th tube.

To each of the 11 tubes add 5 c.c. of colloidal gold solution.

Read after standing at room temperature from 12-18 hours.

INTERPRETATION OF THE COLLOIDAL GOLD REACTION.—A chart can be arranged, similar to the one illustrated (Fig. 12), for the plotting of a curve, to represent the type of reaction present. The changes in color occur all the way from complete decolorization down to slight or no change from the original port or salmon red. Various conditions give different degrees of reactions, but the most typical are graphically represented on the accompanying chart. Normal fluids give no decolorization or, at most, a slight red-bluish tint. General paresis gives practically

Into the 1st tube put 0.25 c.c. of the 0.01% saline solution.

Into the 2d tube put 0.50 c.c. of the 0.01% saline solution.

Into the 3d tube put 1.50 c.c. of the 0.01% saline solution.

Into the 4th to 16th tubes put 1.0 c.c. of the 0.01% saline solution.

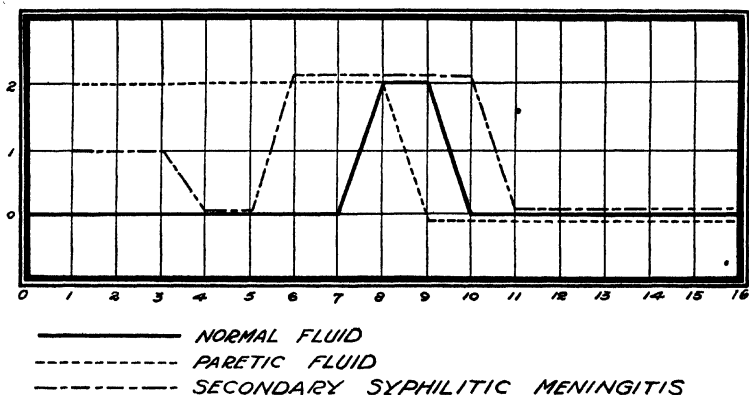
To the 1st tube add 0.75 c.c. of spinal fluid to be tested.

To the 2d and 3d tubes add 0.5 c.c. of spinal fluid to be tested.

Mix and take 1 c.c. from the 3d tube and add to 4th, and so on to the 15th tube. Add none to the control, or 16th, tube.

Add to all 16 tubes 1 c.c. of the colloidal benzoin solution, and shake. Read after 6-12 hours at room temperature.

Complete precipitation with clear upper fluid is called "degree 2," while partial precipitation with opalescent supernatant fluid is "degree 1." No precipitation is "degree 0."



Normal fluids may give precipitation in tubes 6-7-8, but not in the first 5 tubes. The reaction in the first 5 tubes is similar to that in the colloidal gold test.

There are other forms of colloidal reactions, namely, the Colloidal Gamboge Reaction of Riddel and Stewart¹⁵⁰ using a solution of gamboge resin in alcohol; the Berlin Blue Reaction of Kirchberg¹⁵¹ using a 1 per cent. solution of Berlin blue; the Collargol Reaction of Ellinger¹⁵² and Krüskemper using a 1 per cent. colloidal argenticum (Heyden); and Kafka's¹⁵³ Colloidal Paraffin Reaction using a colloidal suspension of pure white paraffin.

The author has had experience only with the colloidal gold test, which he has found eminently satisfactory, and has seen no reason to multiply the number of colloidal tests by the adoption of any of the above.

Cockrill, in a comparison of 400 gold chloride, benzoin and mastic tests, found only 16 dissimilar reactions in all three tests, and found the tests of approximately equal worth. She found the benzoin test simple of preparation, and used it preferentially on this account except in cases of meningitis and multiple sclerosis, where the colloidal gold test is preferable.

CEREBROSPINAL FLUID IN SYPHILIS OF THE NERVOUS SYSTEM

In the late primary or early secondary stage of syphilis, coincident with the dissemination of the spirochete throughout the body, the Wassermann reaction in the blood becomes positive. At this time examination of the spinal fluid in a large percentage of cases studied shows changes in the cell count and globulin reaction indicative of irritation of the meninges. Ravaut,¹⁰³ Altmann and Dreyfuss¹⁰⁴ found in from 70 to 80 per cent. of secondary cases an increase in the globulin content and in the cytologic count above the normal of five to seven cells to the cubic millimeter. In a small percentage of cases in this period a positive Wassermann reaction in the spinal fluid was found, and in most of these patients there were already definite clinical signs of changes in the nervous system. The Wassermann reaction occurring at this time is unquestionably positive proof of involvement of the nervous system by the syphilitic infection. Dennie and Smith¹⁰⁵ in 30 cases of primary syphilis found only 4 cases with mild findings in the spinal fluid (four cells—a trace of globulin). These the writer would consider negative. In none was the fluid positive to the Wassermann test. In 40 cases of *early secondary lues* (roseola present) 8 (20 per cent.) gave positive reactions in the spinal fluid, but one-half of these gave two plus reactions and in the other four 1 c.c. or more of fluid were used; 18 (45 per cent.) gave entirely negative cerebrospinal fluid; 14 (35 per cent.) had mild findings (few cells—mild globulin reaction). In cases of *late secondary lues* (under 2 years' duration) with condylomata lata (in 85 per cent.) or annular eruptions, the spinal fluid was positive in 60 per cent. The clinical evidence was in accordance with these findings; most of the patients complained of headache, had dilated, sluggish pupils, and gave other evidence of meningeal involvement. It is questionable to the writer, however, whether the presence of the positive globulin reaction and increased cell count alone at this time, in the absence of definite objective or subjective nervous symptoms, constitutes *eo ipso* absolute evidence of nervous tissue change other perhaps than a superficial and evanescent meningeal irritation. It is certain that in the majority of these early cases showing spinal fluid changes (pleocytosis, globulin increase) the reaction in the fluid subsequently becomes normal either spontaneously or after treatment. In Dreyfuss's series the reactions persisted in about 12 per cent. of the patients, which corresponds closely to the number of syphilitics who subsequently develop definite involvement of the neuraxis. In the writer's opinion the presence of increased pressure in the spinal fluid in these cases is of doubtful diagnostic significance, owing to the great difficulty of accurately measuring the fluid tension and on account of extreme variations due to extraneous factors, such as the position of the patient, the depth of inspiratory efforts, the size of the needle used for puncture, and its position in the subarachnoid space.

Thus while it is apparent that in early syphilis—active or latent—the only evidence of the presence of spirochetes or their toxins in the nervous system may be found in the biological response in the fluid, it is still a moot question whether the pleocytosis and globulin increase are transient or the forerunners of one of the forms of syphilis of the nervous system. In a number of cases a persistent positive blood Was-

Sermann has led to the discovery of a positive Wassermann in the spinal fluid, increased cells and globulin, without objective or subjective symptoms of neurosyphilitic involvement. These facts doubtless point out the necessity for continued observation and biological examination of patients presenting such changes, and for the prolongation of the period of treatment within reasonable limits, until they are eradicated. This is especially desirable in patients in whom the Wassermann reaction in the blood persists for a considerable period of time after the cessation of treatment and in latent or tertiary cases in which treatment has been neglected. In all these cases lumbar puncture should be done.

Significance of Pathologic Cerebrospinal Fluid in Late Syphilis.

The initial and early secondary periods having elapsed, the patient enters the late secondary and early latent periods, and from this time throughout the later years following the luetic infection the occurrence of a pathologic spinal fluid is of great significance and always indicative of nervous tissue change. The biological response is in the nature of a positive Wassermann reaction (quantities of fluid used in the test 0.1 c.c.—1.0 c.c.), increase in the number of cells (usually lymphocytes) (five to seven cells to the cubic centimeter—normal), and an increase in the globulin reaction of the fluid (as ascertained by the Noguchi butyric acid or other test).

In lesions of the nervous system of the interstitial type (meningovascular) cerebrospinal lues, the Wassermann test of the spinal fluid is positive in from 20 to 80 per cent., depending upon the type and chronicity of the lesion and the amount of treatment received. In the pure cerebral types (Head¹⁰⁶) all the reactions, including the Wassermann, may be negative in nearly all the cases. In the endarteritic types of cerebrospinal lues likewise all the reactions are frequently negative. In the meningomyelitic and meningo-encephalitic types, on the other hand, the reactions are all usually positive. The Wassermann reaction is present in the smallest quantities used, the cells are increased, frequently over a hundred to the cubic centimeter, occasionally a thousand or more, and the globulin is markedly increased (one to two plus). In these cases the pleocytosis and globulin reaction are in direct proportion to the severity of the meningeal inflammation.

In *tabes dorsalis* the spinal fluid is positive at some stage of the disease, and especially early in the disease. The Wassermann reaction is positive in from 70 to 80 per cent. of all cases, the globulin reaction is usually positive, and the cells are moderately increased, rarely being more than a hundred or two to the cubic millimeter. High cell counts—indicative of a marked meningeal inflammation—are uncommon in true *tabes*, and should arouse a suspicion of pseudotabes or of beginning paresis. In the late degenerative types of the disease all the reactions may be and frequently are negative.

In Erb's spastic paraplegia the reactions are apt to be positive early in the course of the disease, but it is the writer's experience that there is a decided tendency toward a rapid subsidence of all the reactions, even without much treatment.

The biological reactions in general paresis are almost always positive both in the spinal fluid and in the blood. The Wassermann reaction in the fluid is positive in the lowest quantities used in the test (0.1 c.c.), the cells are increased to a moderate degree, usually not over a hundred to the cubic millimeter, and the globulin is also increased. The

colloidal gold solution reaction gives the so-called paretic curve, which is regarded as characteristic of general paresis, but which is also occasionally given by other specific and nonspecific nervous conditions, as in tabes and cerebrospinal lues without any signs of intellectual deterioration and occasionally multiple sclerosis. So constant are the above biological phenomena in general paresis that in their absence the diagnosis should be looked upon as unproved unless the subjective and objective symptoms are absolutely conclusive. The few exceptions are found in late degenerative stages of paresis and taboparesis and in the occasional juvenile types, the result of hereditary syphilis.

Clinical Value of Biological Reactions.—Having considered the occurrence of the various biological reactions in the types of syphilitic nervous disease commonly met in practice, a discussion of the value of these reactions in determining the course and prognosis of the disease is essential. The writer is of the opinion that with the rarest exception a positive Wassermann reaction in the blood means the presence of active or latent constitutional syphilis and that a positive Wassermann reaction in the spinal fluid is likewise evidence of an involvement of the nervous system by the syphilitic "virus." A negative reaction in the fluid, however, is not conclusive proof of the absence of nervous involvement nor is a change of the reaction from a positive to a negative one absolute proof of the subsidence or cure of a once existent lesion. In support of the former statement we need only point out the numerous cases of endarteritis of the brain and cord vessels due to syphilis—in which frequently the reactions (Wassermann, cytology and globulin) are all negative in the fluid (and occasionally the Wassermann reaction in the blood also)—and mention the cases of spastic paraplegia and even occasionally tabes and dementia paralytica with negative reactions. Nervous involvement due to congenital syphilis also frequently gives a negative reaction, especially if the nervous involvement occurs late, say after puberty. The occurrence of syphilis of the nervous system of the vessel type in comparatively young individuals, often without marked premonitory symptoms of nervous involvement and with entirely negative biological reactions in the fluid, points out the great care necessary in using a negative fluid as a sign of good omen in prognosis. Lesions of this type cause marked destruction of nervous tissue and correspondingly great disturbance of function from which recovery is only too often impossible. Such cases may give a positive blood reaction, and in the event of a persistent blood reaction in a young or middle-aged individual, with or without some signs referable to the nervous system—as, for example, sluggish pupillary reactions, persistent headaches, optic neuritis, together with evidence of general vascular or renal involvement—the possibility of cerebral vessel change must be borne in mind and proper treatment instituted.

Although all the fluid reactions in cases of spastic paraplegia may be negative, yet the pathologic process may be progressive. The writer has seen a number of cases with marked symptoms referable to the nervous system, in some of which there was a previous history of syphilis but in which all the reactions, both in the blood and in the fluid, were negative, markedly improved by antisyphilitic treatment. In some isolated instances all the reactions may be negative, with the exception of the cytology, which may show an increase above the normal. In a few cases a cell count of five hundred or more lymphocytes to the

cubic millimeter was found and improvement, following intravenous therapy, was rapid. Cases of *tabes dorsalis* and especially *tabetic optic atrophy* not infrequently give entirely negative biological reactions in the fluid and in the blood, with occasionally a slight increase in the cells or in the globulin reaction, yet the symptoms of the disease may be marked and its course progressive. Therefore, the statement of Fordyce,¹⁰⁷ that with all the biological reactions negative in the spinal fluid there is assurance against a relapse in the disease, must be accepted with great reservation. In certain types of cerebrospinal lues, especially of the interstitial or exudative type with superficial meningeal involvement, a progressive change in the fluid from positive to negative is a sign of good prognostic significance, if taken together with progressive clinical improvement of the patient. On the other hand, in cases of this kind where the biological reactions persist in spite of treatment, even though clinically there is marked improvement, especially in the subjective symptoms, the prognosis should be guarded and continued treatment advised. In a certain percentage of cases the Wassermann reaction in the blood persists with or without clinical evidence of involvement of the neuraxis and in these cases no amount of treatment may be successful in changing the reaction. These "Wassermann-fast" cases cannot be treated constantly but should receive gradually decreasing periods of treatment over a number of years.

Instances are not lacking in which the nervous disease has been apparently checked for a great many years in the presence of positive biological reactions, so that one cannot be dogmatic in stating that the persistence of positive biological tests in the blood and fluid is always of bad prognosis. Patients have been treated for a number of years intravenously without affecting the Wassermann test in the fluid; the cytology is usually gradually diminished to within normal limits and occasionally the globulin is also reduced to normal. Finally, after a number of withdrawals of spinal fluid (spinal drainage) the Wassermann reaction, after persisting for a long time as stated, may within a few weeks or months become entirely negative and remain negative for months, gradually relapsing, or may remain negative permanently.

In cases of cerebrospinal syphilis the presence of an isolated symptom often brings up the question as to whether this is a sign of active disease or a residuum of a once existent infection. The stiff and irregular pupil, the absent or diminished knee jerk or Achilles jerk, or a diplopia are examples. In these cases negative biological reactions and the absence of subjective symptoms are presumptive but not absolute evidence of a quiescent or cured process, while the presence of positive reactions in the fluid is contributory evidence of an active, though possibly localized lesion. As regards the effect of treatment in general on the various biological reactions, it may be stated briefly that the cell count in the fluid is usually rapidly influenced by any form of persistent treatment. After one or two intravenous treatments a high cell count from an exudative meningeal process in cerebrospinal lues or pseudotabes may drop almost, if not quite, to normal. Occasionally frequent lumbar puncture has the same effect. The cytologic count is subject to marked spontaneous fluctuations, as Newcomb, Mitchell and Darling¹⁰⁸ have also shown, and even during treatment wide fluctuations may occur. The globulin reaction is less susceptible to change, although on the whole it follows the cell count fairly closely in its variations. The

Wassermann test in the fluid is most constant in its presence and less easily influenced by treatment of any kind than either of the above reactions. In cerebrospinal lues it is most easily affected, and in certain types disappears spontaneously or after treatment with the cessation of the exudative meningitic lesion. In tabes it may be most persistent during the activity of the disease, despite intensive treatment, and may persist up to the very end, or with the onset of marked degenerative lesions the reaction may become negative. Spontaneous fluctuations in the strength of the spinal fluid Wassermann within amounts varying from 0.1 c.c. to 1 c.c. occasionally occur but are uncommon. The persistence of a positive Wassermann in the fluid in the presence of a paretic curve (gold solution) has been interpreted by some syphilologists as a sign of the eventual development of general paresis, but the writer is not inclined to subscribe to this view at present.

In general paresis, treatment may cause diminution in the cell count or globulin reaction, but the Wassermann test is rarely influenced. It rarely even fluctuates but is usually positive in all dilutions, and the paretic curve persists, despite treatment. In late degenerative types of the disease the fluid may gradually become normal; or if treatment is being administered it may be attributed to this fact. This fallacy must be borne in mind in estimating the value of any forms of treatment in this as well as in other types of syphilitic nervous involvement.

RELATION OF SECRETION AND ABSORPTION OF THE CEREBROSPINAL FLUID TO INTRASPINAL THERAPY

It has been asserted repeatedly in support of the rationale of the intraspinal route in the treatment of syphilis of the central nervous system, that salvarsan cannot pass the barrier of the choroid plexus to reach the spinal fluid or the nervous tissue when injected intravenously; hence the direct introduction of the drug into the spinal fluid. The assumption that the spinal fluid is the lymph of the brain and cord is based on the dictum of Mott¹⁰⁹ and Lewandowsky.¹¹⁰ According to Dixon and Halliburton,⁸ the spinal fluid is not an exudation from the blood stream and cannot be considered homologous to the body lymph. Its richness in carbon dioxide is evidence of its excretory function. It is a perfect physiologic medium and its function is protective, acting like a cushion or buffer between the brain and cord and the surrounding bony canal and brain vault, tending to equalize the pressure in the cerebrospinal cavity. A consideration of the secretion and absorption of the fluid makes it clear that substances introduced into the spinal fluid are very rapidly absorbed into the blood stream.

It is agreed by most investigators that the return of the spinal fluid, by way of the so-called pericapillary and perineuronal lymph spaces or sheaths, is a very insignificant one. In fact, the use of the term *perivascular* or *perineuronal lymph space* is more or less fanciful in that it suggests that these spaces contain lymph. In the opinion of Weed these sheaths do not contain lymph, and it is questionable if they serve to carry nutrition to the tissues. They do, however, carry waste matter from the nervous tissue into the spinal fluid, and the direction of the flow, be it noted, is away from the tissues toward the spinal fluid, rather than from the surface toward the cortex or subcortical region. This conception of the perineuronal lymph sheaths is to be borne in

would seem to lie in the discovery of a treponemicidal remedy as readily soluble as the above dyes and able to reach the innermost depths of the nervous tissue in sufficient concentration to act effectually without acting in a toxic manner.

LUMBAR AND CISTERNAL PUNCTURE AS THERAPEUTIC PROCEDURES

Lumbar and cisternal punctures are of definite value in the amelioration of the subjective and objective symptoms due to increased intracranial pressure—headache, vomiting, choked disks, etc. It can hardly be claimed that these procedures by themselves are curative, although, under certain circumstances, the removal of fluid and the coincidental reduction of intracranial pressure promptly cause the complete disappearance of painful symptoms referable to the nervous system and a marked improvement in the patient's general condition. Where intracranial pressure is of such degree as to cause an edema of the optic papillae, the procedures may succeed in temporarily averting blindness, thus allowing time for the institution of decompressive procedures designed to lower intracranial pressure permanently.

In *acute meningitis of microbic origin*, there is always increased pressure and the products of bacterial growth and of tissue autolysis accumulate in the fluid, due to diminished absorptive power coincident with increased pressure. The removal of spinal fluid with a reduction of the pressure to normal permits of a removal of these factors, a re-establishment, if only temporarily, of normal secretion and absorption, and is usually accompanied by a betterment of the clinical condition. In *epidemic cerebrospinal meningitis* and in *tetanus*, the puncture and withdrawal of fluid should be accompanied by the injection of the appropriate antiserum, and the procedure should be repeated as often as the symptoms indicate and in accordance with experience gained in the treatment of this disease. It is a question in the writer's mind as to how much benefit is derived from the use of the antiserum intraspinally and to what extent the withdrawal of fluid and the irritative effect of the serum (usually a foreign protein) on the permeability of the choroid plexus and the secreting mechanism are responsible for the beneficial effects observed in meningitis. That ultimately systemic antibody formation occurs with a transference of curative antibodies from the blood into the tissue of the central nervous system and into the cerebrospinal fluid (aided by the increased permeability of the choroid gland) with a coincidental improvement of the patient's condition, seems beyond question, in view of what has been proven by the experiments of Flexner and Amoss,³⁴ described above.

In *purulent meningitis*—primary or secondary—due to the action of pyogenic organisms of virulent type (*streptococcus*, *staphylococcus*, *Bacillus mucosus capsulatus*, *pneumococcus* and *influenza bacillus*, etc.), lumbar puncture is of symptomatic value only and should be repeated as indicated. If, as a result of adhesions, fluid can not be obtained by spinal puncture, it should be removed by inserting the needle into the cisterna magna. Medication via the cistern route can also be attempted. The use of normal saline and of antiseptic solutions, such as 1 per cent. lysol, weak oxycyanide of mercury solutions, etc., as well as suitable antisera, has been advised, and occasionally cure is effected.

In tuberculous meningitis repeated lumbar puncture with a withdrawal of 30–60 c.c. of fluid or a reduction of the pressure to normal is of decided value in overcoming the symptoms of meningeal involvement, and in clearing up drowsiness and, occasionally, coma. Lavage with saline and antiseptic solutions and the use of tuberculin injections are of doubtful value. Although the prognosis in this type of disease is grave and recovery rare, yet a number of reports of cure have been published, so that in any given case the repeated withdrawal of fluid should be practiced, if only to ameliorate the symptoms and prolong the course of the disease with a hope—if only a forlorn hope—of ultimate recovery.

In *serous meningitis (meningism)*, especially of chronic alcoholism, in chronic nephritis with or without uremia and in acute infectious diseases like typhoid and pneumonia, withdrawal of fluid is sometimes of decided therapeutic value if pressure is increased, and one or two punctures may suffice to clear up cerebral symptoms. Its value in epilepsy, tinnitus, vertigo due to labyrinthine involvement, neuralgias, chorea major, torticollis, herpes zoster, lead poisoning and chlorosis has been affirmed, but is more or less doubtful, though it may be tried if subjective symptoms are marked.

In *hydrocephalus* lumbar puncture has been known to cure the condition, but as a rule its effect is palliative. Unless the factor causing hypersecretion can be controlled, the disease cannot be cured. The removal of, say, 30 to 60 or more c.c. of fluid at stated intervals, by its effect on pressure and absorption, may serve to keep the patient in a comfortable condition and prevent undue hindrance to brain exhaustion in babies. Where the communication between the ventricles and the subarachnoid space is not free, callosal puncture or other operative procedures are to be preferred since lumbar puncture has no effect on the condition.

In *hemorrhage of the brain* from trauma, intracranial pressure may be excessive and the careful withdrawal of fluid is indicated, the pressure being lowered gradually to within, say, 30 to 60 mm. of water of normal limits, provided symptoms of intracranial pressure exist. After the acute symptoms of an apoplectic attack have subsided, a carefully performed lumbar puncture may be not only of diagnostic but also of therapeutic value, especially in the presence of symptoms of increased pressure. The sudden lowering of pressure in patients with diseased cerebral vessels is to be avoided. In hemorrhage of the spinal cord due to trauma the procedure is of value especially in the presence of symptoms of cord compression. In all the above conditions puncture should be done only after due consideration of all the facts in the case and provided there is a definite indication for the procedure.

Tumors of the brain are usually accompanied by high intracranial pressure; and measures for the relief of the symptoms as well as to avert the progress of choked disk, which rapidly proceeds to complete blindness, must be speedily carried out. Pending the performance of a cranial decompression, a very carefully performed lumbar puncture with gradual reduction of fluid not quite to normal limits is indicated. As was mentioned before and will bear repetition, the suspicion of or presence of tumor in the posterior fossa adjacent to the pons or medulla, calls for the greatest care in the performance of the puncture. A manometer should be used and the stylet of the needle must be withdrawn slowly. The patient's pulse and respiration should be carefully

watched and the first signs of respiratory embarrassment or headache should call for an immediate cessation of the puncture and, if necessary, the institution of artificial respiration and other necessary measures.

In *syphilis of the nervous system* the withdrawal of cerebrospinal fluid is of decided symptomatic value, especially where intracranial pressure is increased. Persistent headache and vomiting and even drowsiness and impending coma as a result of increased tension are frequently rapidly cleared up in a remarkable manner. The procedure may be repeated as indicated. In papillitis, with impending blindness from intracranial gumma, the indications for withdrawal of fluid, cisternal puncture and cranial decompression are the same as in tumor cerebri. In a series of independent studies, as yet unpublished, the writer and Kuttner confirmed the work of Barbat,¹¹⁵ who states that after intravenous injections of arsphenamine arsenic is found in the spinal fluid within twenty-four hours and in most cases shortly after intravenous injection. He believes that the reduction of intraspinal pressure by withdrawal of large amounts of spinal fluid (30-60 c.c.) increases the permeability of the meninges by the causation of a congestion, the dilated capillaries permitting the passage of their contents with greater freedom.

Kaliski and Strauss¹¹⁸ believe that in certain cases of syphilis of the nervous system the repeated injection of arsphenamine followed by withdrawal of cerebrospinal fluid in large quantity is of decided therapeutic value.

THE MENINGITIDES: DESCRIPTION AND DIFFERENTIATION

In the various clinical forms of inflammation of the meninges there is usually involvement of the pia mater and arachnoid, and the cerebrospinal fluid is cloudy, turbid or frankly purulent. The various organisms giving rise to the inflammatory processes were enumerated under the heading Bacteriology of the Cerebrospinal Fluid in this section. Meningitis has been described in the following conditions, or the specific organisms of these diseases have been found in the affected fluid: tuberculosis, meningitis, pneumococcal pneumonia, streptococcus and staphylococcus infections, influenza, typhoid fever, plague, anthrax, blastomycosis, mumps, typhus fever, Malta fever, trichinosis.

The degree of change in the spinal fluid is in direct proportion to the intensity of the inflammation and to the extent of involvement of the membranes. In rare instances of localized inflammatory processes and in ventricular inflammation without communication with the subarachnoid space from closure of the foramina of Magendie and Luschka, the fluid obtained by puncture in the lumbar region may be quite clear and normal. In the vast majority of cases of inflammation of the meninges due to the pyogenic bacteria, the fluid is turbid or purulent, due to the outpouring of polymorphonuclear cells; there is a definite increase in the protein content of the fluid; pressure is increased, chlorides are diminished progressively, and the carbohydrate tests show the absence of sugar. Organisms may be demonstrated in spreads of the fluid stained appropriately, or by culture. Occasionally it is not possible during life to demonstrate organisms in spreads or in culture, even after prolonged examinations. The causes of purulent meningitis are merely mentioned to indicate the value of an examination of the fluid in differential diagnosis. They are general sepsis, diphtheria, scarlet fever,

measles, sinus inflammation, influenza, erysipelas, otitic disease, abscesses, osteomyelitis; in rare instances tuberculous meningitis may be accompanied by very cloudy or turbid fluid and the outcome of the examination of the fluid must be considered in conjunction with the clinical conditions present, if the laboratory tests are to have their fullest value in differentiation.

Traumatic causes are not uncommon in these conditions. Injury of the brain or cord may be followed by direct infection of the meninges, or the latter may be secondarily infected. *Cerebrospinal meningitis* due to the diplococcus of Weichselbaum or meningococcus is considered elsewhere. *Otitic meningitis* is a most common form of septic involvement, and in otitis media and its train of sequelæ—mastoiditis, sinus thrombosis, dural abscess and abscess of the brain—the state of the fluid, whether clear, turbid or frankly purulent, and the absence or presence of organisms are of the greatest importance in diagnosis and prognosis. A frankly purulent fluid with organisms speaks for a *diffuse septic meningitis*, with subarachnoidal or subdural abscess or ruptured abscess of the brain; a turbid fluid without organisms brings up the question of *meningitis sympathica*, while a clear fluid points to the *absence of acute meningeal inflammatory involvement*. With evidence of mastoid disease and a clear fluid, and a positive blood culture, the presence of *sinus thrombosis* is almost certain. If meningeal symptoms are present they can be explained by the presence of *meningeal irritation*, especially if there is an increase in the lymphocytic elements in the fluid. Where the fluid has been positive for organisms and the symptoms progress but the organisms disappear from the spinal fluid, the possibility of closure of the foramina of Magendie and Luschka must be borne in mind.

In *serous meningitis* there is a definite hypersecretion of fluid. This is commonly seen in the wet brain of alcoholics, in uremic cases and in sunstroke. The fluid is usually normal, occasionally showing a slight increase in lymphocytes. In the *meningism of infectious diseases*—especially pneumonia and occasionally in typhoid fever—the fluid is of the same character unless there is a direct inflammatory lesion of the meninges, in which event the fluid is purulent.

In the more *chronic forms* of meningeal inflammation, notably in *syphilitic involvement of the meninges*, the process is much less intense, hyperplastic or exudative, and the fluid is usually clear or at most faintly clouded. There is a tendency in the more chronic conditions for the lymphocytic elements to predominate in the fluid. This is true also of *tuberculous meningitis* where the degree of clouding is in proportion to the number of cells present in the fluid. Frequently the fluid is quite clear with just a few flakes of fibrin, in which the tubercle bacilli can be demonstrated. In a few instances the polymorphonuclear cells predominate during the early days of a tuberculous meningitis, but usually give way eventually to the characteristic mononuclear cell. The changes in the fluid in syphilis have been considered in detail in another part of this article. Slight changes in the fluid characteristic of chronic inflammatory processes are occasionally described as occurring in senile dementia, chronic lead poisoning and chronic pachymeningitis, but in the writer's experience the fluids in these conditions fail to show anything worthy of note. Excepting for a marked increase in pressure and hypersecretion, there is no definite change in the spinal fluid of chronic *basilar meningitis*.

Meningitis Sympathica.—Meningitis sympathica is a condition described by Plaut, Rehm and Schottmueller¹²³ in which, in response to a process contiguous to the membranes but not actually involving them, there is a definite change in the cerebrospinal fluid with marked symptoms of meningitis. The fluid is found to be increased in pressure, globulin is increased, and there is a definite clouding or turbidity due to the presence in the fluid of polymorphonuclear cells or, less frequently, of lymphocytes. In this condition the fluid is invariably sterile, no organisms being found either in spreads or on culture.

DIFFERENTIATION FROM OTHER FORMS OF MENINGITIS, ETC.—It must be differentiated from *meningitis aseptica*, so-called, which is a true inflammatory process from other than bacterial causes, involving the membranes, while in meningitis sympathica there is a diapedesis of cells through the pia arachnoid without demonstrable changes in the membranes. A true meningitis aseptica can be produced by the intraspinal injection of foreign sera, medicaments or by the injections of saline solution or of air. Meningitis sympathica clinically and biologically simulates a meningitis, but pathologically is not a meningitis. If we accept the explanation of the escape of the meninges in this condition we must to a great extent alter our views, first promulgated by the French school of Sicard, Ravaut and others, that lymphocytic pleocytosis is to be looked upon as an evidence of meningeal irritation, while polynucleosis is evidence of a true inflammatory process, especially if there is in meningitis sympathica a turbid fluid from marked outpouring of cells. Quinke¹²⁴ looked upon cases of meningeal irritation without anatomical evidence of inflammation of the meninges as a result of chemical toxins acting directly on the central nervous system. Nissl¹²⁵ believed that a circumscribed inflammation could occur without changes in the cerebrospinal fluid, provided the overlying arachnoid was not involved. According to Nissl, in the hyperplastic form of meningitis without cellular exudate, no cellular changes are observed in the fluid, but where a cell increase is observed in the fluid prolonged search usually reveals changes of an exudative character in the meninges. Voisin more recently has shown that in the early stages of a true meningitis there is acute meningeal congestion with the production of what has been termed a serous meningitis. The pressure of the fluid is increased but there is no increase in protein until later, when bacterial invasion has commenced. The fluid is under great pressure, becomes turbid, protein becomes increased and, finally, bacteria are found in the fluid. Before the fluid becomes infected, chlorides and glucose are not materially diminished and form valuable differential points. Now meningitis sympathica clearly differs from this so-called *serous or edematous meningitis* or from the early stage of acute meningitis, not only in its course but in the conditions giving rise to it. It might be well to reserve the term *meningitis aseptica* to cases caused by mechanical irritation of the meninges, using the term *serous meningitis* for the secondary ephemeral conditions with congestion or edema of the pia arachnoid, arising in the course of infectious diseases, and in uremia and alcoholism in which the fluid is not changed in character. In the differentiation of meningitis sympathica and meningitis aseptica as generally accepted—as Strauss¹²⁶ pointed out—the presence or absence of an inflammatory focus in the cranium will often determine which type we are dealing with.

One of the most frequent causes of meningitis sympathica is brain

abscess following middle ear disease with or without mastoid or sinus complications, or intracranial abscess from any cause. Ruprecht reports the autopsy findings of a case of abscess of the temporal lobe without meningitis in which the spinal fluid was sterile and cloudy. The condition may occur as a result of inflammation of the accessory sinuses, sphenoidal cells, ethmoidal cells, etc. In a case of orbital cellulitis following trauma, cited by Strauss,¹²⁶ frontal lobe abscess was suspected, the spinal fluid was sterile and turbid, and the abscess was found at autopsy, although the surgeon at operation failed to locate it. In some cases the condition may be a forerunner of a true inflammatory meningitis with bacterial invasion, but it is doubtful if this condition is a healed stage of a bacterial inflammation of the membranes. In a certain number of cases meningitis sympathica was present without any clinical symptoms of meningeal involvement; i.e., the fluid was turbid and sterile and under increased pressure, hence the advisability of performing lumbar puncture in the conditions enumerated above, which may be accompanied by intracranial suppuration. In mastoid disease or sinus thrombosis the persistence of the cloudy fluid under pressure without organisms proves that the suppurative focus is in the epidural region contiguous to the membranes, and has probably not been evacuated by the operative procedure undertaken. If the fluid early is cloudy and later becomes frankly purulent, with or without the presence of organisms, it is likely that the pus has ruptured into the ventricles or into the sub-arachnoid space. In one such case Strauss found Gram-positive organisms in spreads, but these did not grow in culture and at autopsy a ruptured abscess cavity was found.

Instances of meningitis with sterile spinal fluid are not rare. Mýgind¹²⁷ has reported such cases, which were confirmed at autopsy. In other cases the organisms are found late in the disease or only in the ventricular fluid. In such old cases there is apt to be a greater amount of pus in the fluid and the cells have undergone autolytic changes with the appearance of vacuoles and the disappearance of granules, but the polymorphonuclear cells persist; while in late stages of meningitis sympathica the changes in the cells are not so marked, and eventually lymphocytes may replace the polymorphonuclears.

Cerebral syphilis is differentiated by the outcome of the Wassermann tests and by the efficacy of antisppecific treatment. *Tuberculous meningitis* offers more difficulties of differential diagnosis unless there is a known focus of inflammation present, e.g., in the ear. But in tuberculous meningitis the fluid is usually less turbid, more often contains lymphocytes; and tubercle bacilli, if found, clinch the diagnosis. Except during epidemics and until localizing signs appear, differential diagnosis from *poliomyelitis* and *encephalitis* will be difficult, especially in abortive cases of the former. The presence of a known focus of suppuration in meningitis sympathica and the course of the case in poliomyelitis and encephalitis will eventually make the diagnosis. After hemorrhage, when most of the blood has been absorbed, a few lymphocytes may remain and offer slight difficulty in diagnosis, but the persistent tinge of yellow in the fluid is significant. In *brain tumor* adjacent to the membranes, focal symptoms must be relied upon for diagnosis.

Acute Anterior Poliomyelitis.—The spinal fluid shows distinct changes in the early stages of acute anterior poliomyelitis. It is already changed during the first week, containing an increased number of cells;

the pressure may be moderately or greatly increased; and, on standing, a fine, web-like clot may form. If the cells are greatly increased the fluid, instead of being clear, shows a "ground-glass" clouding. Usually there is a moderate increase in cells, up to 100 or 200, but occasionally 600 to 1,000 or more to the cubic millimeter may be found. The predominating type of cell is the lymphocyte, but frequently in the early days, especially in the preparalytic stage, polymorphonuclears may predominate to the extent of 80 per cent. or more. Occasionally large phagocytic cells with vacuoles are to be seen. According to Peabody, Draper and Dochez,¹²⁸ the highest cell count is obtained in the early stage of the disease, with a gradual falling off as the disease progresses. The globulin is usually slightly increased during the first week, gradually increases in amount during the second and third weeks, and may persist long after the acute symptoms have passed away. Out of 69 cases studied by these authors only two cases showed normal fluids throughout.

Bacteriologically the fluid may be said to be negative. Organisms have been described in the fluid by Rosenow and others, but as yet these findings have not been accepted as final evidence of the etiological relationship between the bacteria found and acute poliomyelitis. Chemically, aside from the slight increase in globulin, the fluid shows no change from the normal. Complement-fixing bodies have not been demonstrated in the fluid of these cases, although studies have been made both on human and animal serum by Römer and Joseph,¹²⁹ Gay and Lucas,¹³⁰ Wollstein,¹³¹ Kaliski and Strauss, and others. The results of Neustadter and Banzhaf,¹³² in the opinion of the writer, are not conclusive of the presence of such bodies.

Early diagnosis, especially before the appearance of paralytic signs, is facilitated during epidemics by the finding of a clear or slightly turbid fluid with a marked increase in cells, polymorphonuclears predominating before the appearance of paralysis, and a slight increase in globulin; or by the finding of a moderate increase of cells, with a lymphocytic prevalence and a slight or moderate increase in globulin. These cases—especially of the abortive type or in the preparalytic stage—must be differentiated from tuberculous meningitis, in which there is much less frequently an increase in polymorphonuclears and in which tubercle bacilli can usually be found, and from other types of meningitis. The differential diagnosis from *meningitis sympathica* has already been mentioned. From *encephalitis*, especially the type known as *encephalitis lethargica*, poliomyelitis can be differentiated, not on any definite differences in the fluid—for the fluids may be alike—but on the prevalence of paralyzes of the ocular muscles and involvement of the base of the brain, especially the cranial nerves, combined with the marked drowsiness. It is not always easy to differentiate *anterior poliomyelitis* in the adult from *meningomyelitis of syphilitic origin*. In a case of this type seen by the writer the paralysis occurring during an epidemic was almost typical of poliomyelitis, but the positive Wassermann in the fluid and in the blood, together with increased cell count and globulin, and the response to treatment left little doubt as to the true nature of the infection.

Trichinosis.—The *Trichina spiralis* has been found in the cerebrospinal fluid by Van Cott and Lintz⁸⁸ in a case that resulted fatally. Among other typical symptoms of the disease, marked nervous symptoms suggestive of meningeal involvement were present, and trichinae

were found in the fluid. The fluid was under moderate pressure, contained a trace of albumin, and on standing showed a grayish white sediment. Fehling's solution was not reduced. Microscopically lymphocytes and actively motile trichinæ, 1 mm. in length, were observed. No parasites could be found in the blood but the muscles contained large numbers. According to these authors the nervous symptoms are due not only to the toxemia but to the mechanical pressure on the brain and cord by the trichinæ. Subsequently Lintz reported three additional cases. The trichinæ were found actively motile in the fluid and kept their motility at room temperature for three days.

THE CEREBROSPINAL FLUID IN NEUROLOGY AND PSYCHIATRY

In the diagnosis and prognosis of disease of the central nervous system, the examination of the cerebrospinal fluid has perhaps its field of widest application and greatest utility. The modern neurologist is dependent upon the facts elicited by such an examination in the vast majority of patients who present themselves to him, in order to supplement or substantiate the clinical diagnosis. The symptomatology of organic and functional nervous involvement is so protean and the differential diagnosis between the organic and the functional often so difficult, even after prolonged observation, that scientific physicians are learning to call upon the laboratory more and more often for help. By means of a careful analysis of the data ascertainable by examination of the cerebrospinal fluid supplemented by the serological examination of the blood, we are able to determine with a fair degree of certainty in many cases whether we are dealing with an organic or a functional disease, whether the organic disease is of an inflammatory nature, acute or chronic or neoplastic; and when the lesion is organic in nature, we can frequently determine the etiological factor, e.g., in syphilis, tuberculosis, suppurative conditions, etc. New facts are constantly being added to the sum of our knowledge, and with increased clinical experience the correlation of the subjective and objective factors and the data obtained by chemical, bacteriological, physiological, cytological and serobiological examination are more accurately and readily applied in the scientific study of disease of the central nervous system.

Syphilis is an extremely important factor in the etiology of disease of the central nervous system and methods for its detection have been considered in detail under a separate heading (p. 527). It is superfluous to emphasize again the importance of and necessity for examination of the cerebrospinal fluid in the diagnosis, prognosis and treatment of the syphilitic diseases of the neuraxis. The syphilitic factor in nervous disease is so frequently present and the clinical picture so often mistaken for a functional nervous involvement or for an organic condition of nonspecific character, that it is wise to resort to serological examination of the blood and cerebrospinal fluid when there is the least suspicion of the possible presence of this disease. Indeed, in institutional practice, the collaboration of the laboratory should be invited in every new case admitted to the wards. It is necessary, at this point, to repeat the advisability of bearing in mind the fact that occasionally—if only exceptionally and rarely—the serological examination may be entirely negative, or perhaps but one factor in the complete serological scheme

may be present, e.g., an increased number of cells or increased globulin content, in the presence of syphilis. Therefore, instead of ruling out the presence of syphilis of the nervous system because of such negative findings, the clinician—if his suspicions are aroused by his study of the clinical picture of the case—is justified in resorting to antisyphilitic treatment in order to determine the influence of such a therapeutic measure in the course of the disease. Combined with this procedure the serological examination may again be undertaken to determine whether a provocative reaction either in the blood or possibly in the cerebrospinal fluid has been elicited. In any event it cannot too frequently be reiterated that a negative serological examination does not necessarily exclude syphilis.

Under separate heading the *acute and chronic inflammatory lesions of the neuraxis* have been considered in detail. In passing to a consideration of the more chronic organic and functional nervous diseases, it may be stated that while the more acute lesions are apt to make their presence known by a certain degree of inflammatory reaction on the part of the membranes, with changes in the fluid which have already been described, this is not invariably the rule and occasionally a normal fluid is found under circumstances that lead the clinician to believe he is dealing with an acute condition. In certain of these cases the communication between the ventricle and the subarachnoid space is interrupted at the exit of the fluid from the 4th ventricle; in others, as in certain types of disease that show a predilection for the gray matter rather than the coverings, for example, acute polio-encephalitis and poliomyelitis, there is little, if any, meningeal change.

So far as the cell count in the cerebrospinal fluid is concerned, the neurologist is aware of the fact that in the majority of cases of acute inflammation of the membranes the polynuclear cell predominates, while in the more subacute and chronic conditions the small lymphocyte is present in predominating percentages. To this there are exceptions, as, for example, in cases of tuberculous meningitis and in poliomyelitis; while in the spirochetal diseases of the neuraxis the lymphocyte almost always predominates.

In most *chronic organic diseases of the nervous system* of nonsyphilitic origin the cerebrospinal fluid shows little, if anything, of positive value from a diagnostic standpoint. The findings are of some value in a negative sense. In *lateral sclerosis, amyotrophic lateral sclerosis, combined sclerosis, the progressive muscular atrophies and the muscular dystrophies*, and in *syringomyelia* there are no characteristic findings in the fluid. Occasionally in multiple sclerosis the cells (lymphocytes) are increased slightly above the normal—rarely above 10–15 to the cubic millimeter—and where a larger number of cells is found, it is prudent to look for some etiological factor—possibly syphilis—or neoplasm to account for the pathological process for the clinical picture present. With the colloidal gold test the fluid of multiple sclerotics occasionally gives a curve quite similar to that obtained in the fluid of general paretics. The Wassermann reaction, both in the spinal fluid and in the blood, is negative, however, unless the sclerosis is of syphilitic origin. In a case of supposed multiple sclerosis with typical objective findings and clinically undistinguishable from multiple sclerosis, the finding of a positive blood and spinal fluid reaction led to the correct

diagnosis and antisyphilitic therapy was followed by marked improvement in the symptoms.

In *paralysis agitans*, *chorea* and *related syndromes* the cerebrospinal fluid is negative. In a series of more than fifty choreic patients a positive Wassermann was not obtained in a single instance, contrary to Milian. In the various *cerebellar syndromes* the cerebrospinal fluid is normal unless hemorrhage is the cause of the condition, in which event the fluid may be bloody or tinged with blood or changed in color, as described under hemorrhage involving the cerebrum. In *vascular disease of the brain* there is, as a rule, a negative fluid. In *arteriosclerosis* of the vessels of the brain and cord there is usually no change. In such conditions, if lumbar puncture is indicated, it should be done with the greatest care, the fluid being removed very slowly, the manometer being utilized to prevent too marked or too sudden a drop in pressure. If the fluid under these conditions is under great pressure, it should be reduced, not to normal, but to within 50 or 60 mm. of the average normal point.

Chronic organic involvement of the nervous system of nonsyphilitic origin seems to follow in the wake of the influenza scourge—a definite number of the cases, even where there is no clinical evidence of meningitic involvement, show an increase in cells (usually the small lymphocyte predominating), the number ranging from 10 to over 200 cells to the cubic millimeter. This disease is somewhat similar in its pathological picture to poliomyelitis and, like the latter, shows a change from the normal in the fluid only in cytology and less frequently in the increased globulin content.

In *hemorrhage of the brain* from rupture of vessels due to trauma or apoplexy, bloody fluid is obtained if the hemorrhage occurs into the ventricle and if the foramen of Magendie and the foramina of Luschka are not blocked. This subject has been discussed in detail under the heading Xanthochromia. Lumbar puncture is rarely resorted to in the diagnosis of apoplectic attacks and is a procedure to be undertaken with great circumspection and only when absolutely necessary to aid in diagnosis. In vascular lesions of the brain and cord due to trauma lumbar puncture is of decided diagnostic value.

In *abscess of the brain* the cerebrospinal fluid may be entirely normal. If, however, the abscess is contiguous to or involves the membranes or ruptures into the ventricles, the cerebrospinal fluid either contains a definite increase in the cellular elements or may be decidedly purulent. This subject is considered in greater detail under the heading Meningitis Sympathica.

In *tumors of the brain* the fluid may be the seat of definite changes, although in many cases there is not the slightest change, except perhaps in the pressure. By interfering with absorption of the fluid, tumors may cause a marked rise in intracranial pressure with all the concomitant symptoms of this condition, viz., choked disks, headache, vomiting, vertigo, etc. This is especially apt to be the case if the tumor is subtentorial and of sufficient size to cause pressure and secondary hydrocephalus. Frequently, however, the pressure is normal or only slightly increased in tumors of the brain. One rarely obtains changes in the cellular or protein content of the fluid. *Gummata* of the brain may cause the same mechanical conditions as other tumors and occa-

sionally produce, in addition, changes in the Wassermann cytology and globulin characteristic of syphilis.

Tumors of the spinal cord frequently produce characteristic and diagnostic changes in the fluid which have been considered in detail under the heading Xanthochromia. There is an increase in cells and globulin, a characteristic lemon-yellowish color and occasionally the fluid coagulates spontaneously within a short time after withdrawal. The Nonne-Froin syndrome and the variations in the factors just described are also considered in greater detail under the above heading. Froin's syndrome is characteristic of lesions of the cauda equina and is occasionally the result of adhesive inflammatory lesions of the membranes in this region. In early cases a very heavy increase in globulin may be obtained without definite cell increase, and there may be little or no color change. This is more apt to be the case in extramedullary growths.

True *idiopathic epilepsy* produces no fluid changes. Epilepsy may be caused by syphilis, in which case the fluid gives a positive Wassermann with increased cells and globulin and frequently a positive reaction in the blood. In adults the advent of epileptiform seizures should arouse a suspicion of general paresis, especially in the presence of positive biological reactions.

In *alcoholism* the fluid may be under marked pressure, though changes in the fluid are infrequent. In the presence of a decided increase in cells and of globulin, with or without a positive Wassermann reaction, the suspicion of a luetic factor should be entertained.

In *postdiphtheritic paralysis* the author has failed to find any departure from the normal, with the routine tests. Regan,¹⁵⁵ in a review of the literature, states that the fluid in this condition is clear, under normal or moderately increased pressure, with rarely an increase in proteins, normal glucose figures, with normal cytology, the chlorides ranging from 7.1 to 7.9 grams per litre. The colloidal gold reaction shows little if any departure from the normal, and in none of the cases reported could either toxin or antitoxin be detected in appreciable quantity in the fluid.

In the differential diagnosis between functional and organic nervous disease, lumbar puncture and the facts elicited by an examination of the fluid play an important rôle. In the diseases of the psychical system—the neuroses, the psychoneuroses and the true psychoses—the fluid is normal. Recently, however, Mestrezat¹⁵⁶ found in a study of so-called shell-shock cases that 80 per cent. of the fluids gave an abnormal secretion and an increase in the protein content of the fluid. This condition of the fluid was found within two to three days of the onset of the shock and did not subside for weeks or months. In the opinion of Mestrezat it testified to the organic nature of the disease. At least it points to a possible organic change in the secreting mechanism, if not to definite pathological change in the nervous tissue.

Where changes are found in the fluid, especially if the clinical symptoms are not well defined or characteristic, a suspicion of organic disease must be entertained. It is well to bear in mind that in certain cerebral conditions of syphilitic origin, especially in cerebral endarteritis, one is apt to encounter entirely negative findings in the fluid and in the blood. But other clinical evidence of syphilis is rarely totally lacking to aid in the differential diagnosis between a functional condition

or a neurosis or psychosis on a syphilitic basis. General paresis, unless it is in the late degenerative stages, rarely presents a negative blood and entirely normal fluid, so that such examinations are of great help in the differential diagnosis between certain types of dementia precox with marked mental deterioration and true paresis. Constitutional syphilis may be combined with a nonsyphilitic mental disease. A persistently negative cerebrospinal fluid in the absence of signs of nervous involvement, as, for example, in the pupillary and deep reflexes and changes in the fundi, should point to this conclusion. In doubtful cases the patient deserves the benefit of antisyphilitic treatment and a repetition of the tests.

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548 CEREBROSPINAL FLUID IN HEALTH AND DISEASE

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CHAPTER XII

CASE HISTORY TAKING

BY ARTHUR F. BYFIELD, PH.B., M.D.

General considerations, p. 551—Materials, p. 561—The history proper, p. 572—Present illness, p. 572—Previous illnesses, p. 578—Family history, p. 581—Personal routine, p. 583—Venereal history, p. 585—Menstrual history, p. 586—Symptoms noted by the examiner while taking the history and before beginning the examination proper, p. 587.

GENERAL CONSIDERATIONS

A first-class history is a necessary prelude to a first-class diagnosis; in some cases, indeed, a well-elaborated anamnesis practically establishes the diagnosis. The converse is equally true—a history, written hurriedly and aimlessly, composed of data not properly digested or analyzed, is not only valueless but often highly misleading.

Case-taking is both an art and a science, and reflects to the very highest degree the skill, judgment, tact and breadth of clinical experience of the recorder, particularly the latter, we may say, as it is only on the basis of a fairly ripe experience that a really valuable case history is possible.

To the young physician just launched upon his clinical career this may sound discouraging. He may wonder how, with only the most meager bedside experience to support him, he can pretend to prepare a satisfactory medical history. Until recent years, indeed, such a question would have been fully justified, as the methods of teaching medicine formerly in vogue—and in too many schools at the present date—permitted the medical student but little personal and responsible contact with the patient. The result of these older methods was that, with but few exceptions—the brilliant clinicians and teachers who understood the indispensable aid offered by a properly written history, and who laid emphasis upon the principles of the subject—the student graduated with only an occasional hint relative to case-taking, in the dispensary or clinic, and too often with not even this hint. These men, as practitioners, were apt to disregard the value and importance of a history altogether and to make use of slipshod methods, to which reference will be made later.

In the better schools this has, to a large extent, been changed. The patient is given to the student *as a case*, in his clinical years, and, by means of clinical clerkships in the dispensary and hospital and of small,

bedside clinics, he is expected to develop a diagnosis from beginning to end. It need not be said that proper instruction presupposes a careful supervision, on the part of those in charge of such work, not only of the diagnostic routine, but also of the details of the anamnesis.

In brief, it may be said without exaggeration that the character of a medical school may be gauged with a very fair degree of accuracy by the caliber of the histories written by its graduates; while, in the case of the man in practice, it is not difficult, on the basis of the kind of history he prepares, to estimate not only the character of his early training, but also the breadth of his subsequent clinical experience.

The graduate of the higher type of medical school is, in still other ways, better equipped from the outset to write a good case history, thus compensating to some extent for the experience and judgment that come only with years. We refer first to the fact that some schools include in their curricula didactic work on the preparation of medical histories—this being the subject, primarily, of this chapter—and, secondly, to the fact that in the more advanced colleges the student is so thoroughly grounded in pathology and pathologic complexes that he is in a position, as will appear in the following pages, to direct his questions to the patient in such a manner as best to develop the data essential to a diagnosis.

The well-trained physician—one who has had some grounding in the fundamentals of what constitutes an acceptable history, and who, under proper instruction, has had a fair opportunity of applying these fundamentals in actual clinical work for which he is held responsible—will not find it altogether difficult to separate the valuable from the worthless in case histories. This difference is by no means one of length, as so many seem to believe; *brevity*, indeed, when combined with the faculty of searching out the important and of analyzing the same, is one of the *prime essentials of a good history*. The uninformative anamnesis is one the only merit of which is that it adheres to a set outline: symptoms are jotted down and left hanging, as it were, without coherence and coördination in the fabric as a whole; invaluable diagnostic points are omitted, either because the questioner is too inexperienced to ask salient questions, or because one or more answers of the patient have caused him to pass premature judgment upon the case.

A history becomes increasingly valuable as it aids in the making of a diagnosis. It is true, as we shall see later, that a definite scheme is necessary in the routine of obtaining the patient's story; but, aside from this guiding outline, each anamnesis should have its individual stamp. Just here lies the pernicious influence of the all too general habit of employing printed outlines in which a fixed space is allowed—determined to some extent by the printer and also by the size of the card or sheet employed—for the recording of the several subdivisions of the history. A worth-while anamnesis, brief and to the point though it must be, cannot be cramped within set confines. In some cases, the *complaint upon entrance* may demand only a few lines and the recording of *previous illnesses* half a page. How, then, can one do oneself or one's patient jus-

No.	Case	Diagnosis
Name.....	Age..... Nat.....	Dom. Rel..... Occup.....
Family History		
Personal History		
Habits.....	Alcohol.....	Tobacco..... Venereal.....
Previous Diseases.....		
Present Complaint.....		
Status Praesens. Weight..... Height..... Temp..... Resp..... Pulse.....		
Physical Exam.		
Facies, Eye.....	Conj.....	Pupil..... Light React.....
	Ocular mov.....	Accom..... Conv.....
Mouth.....	Tongue.....	Teeth.....
Pharynx.....	Tonsils.....	Thyroid.....
Glands.....	Sub. Max.....	Cerv..... Axil..... Cubital.....
Lungs.....		Left
Inspection.....	ANT.....	POST.....
Apices.....		
Boundaries.....		
Adhesions.....		
Percussion.....		
Palpation.....		
Auscultation.....		

FIG. 1.—CARD ILLUSTRATING A POORE METHOD OF RECORDING THE MEDICAL HISTORY AND THE DATA OF THE EXAMINATION.

Records of this type are in very general use, but are practically worthless.

tice when under the restrictions of printed forms such as are all too commonly employed (Fig. 1)? The chief justification for using them would seem to be that they are a sort of prop for the student or physician who has had no adequate instruction in the writing of histories, and whose training has led him to regard the patient as a case, not as an individual.

While discussing the matter of stereotyped forms for the writing of the history proper, we may at this time conveniently call attention to a no less objectionable custom of employing "cut and dried" outlines for the recording of the physical and laboratory examinations (Figs. 1 and 2). The particular card chosen to illustrate this point, although possibly an exaggerated example, possesses the objections common to all such forms, first, that they arbitrarily limit expansion where expansion is necessary, and secondly—particularly in the case of the more elaborate forms—that they suggest a routine for examination which is rarely called for in an average case. It is not necessary, for instance, when a patient from a malarial region presents himself with a history of regularly recurring chills, fever and sweats, to determine whether his auditory canal contains inspissated cerumen, or whether his sense of coördination is normal, in order to fill in the spaces devoted to these questions on some cards of this character. Occasionally, one encounters a case in which all of these minutiae must be observed; as a rule, however, the patient's story, carefully analyzed, should serve as a guide to the course of the physical examination. (By way of contrast with Figs. 1 and 2, see Fig. 3.)

The author does not for an instant wish to give the impression that a *thorough* examination should not be made in every case, no matter what the complaint. What he does intend to convey is that the history sheet, in addition to points essential to every examination, should not contain a mass of irrelevant material such as would necessarily be embodied in a printed form applicable to all cases. It adds nothing to the findings in a clean-cut case of duodenal ulcer to have noted upon the sheet in the blank reserved for eye-muscles that the latter are normal.

A complete, but not padded, history and examination are necessary in every case. It may also be noted that, although the major part of what is to be said here applies with especial emphasis to medical cases, it is true to a scarcely lesser degree that a full history and a thorough *general* examination are necessary in surgical, gynecologic, dermatologic and other conditions. There is nothing truer in diagnosis than this: The average physician who prepares a careful history and makes a complete routine examination will arrive at a greater number of correct diagnoses than will his more brilliant colleague who glides over the patient's anamnesis, makes a snapshot diagnosis on the basis of the incomplete information he has received, and directs his physical examination along the lines of his premature judgment.

Accuracy is, of course, one of the prime essentials of a history which is of value, and a great many factors enter into consideration in this connection. In the first place, one must allow oneself sufficient time. To attempt to cut short the anamnesis, because one is busy, leads to two

things—a loss of the very necessary meditative aspect on the part of the physician, and a hindrance to the full play of the patient's memory. On the other hand, the voluble patient, once his peculiarities are understood and appreciated from the point of view of their diagnostic significance, should, by tactful counterquestions, be interrupted in order that time should not be wasted.

In the matter of accuracy, further, it is obvious that the examiner must be conversant with the language of the patient. Little difficulty will be encountered on this score in the average practice, for if a physician hangs out his shingle in a community where a foreign tongue prevails, it is almost a *sine qua non* to know that tongue. In the larger general hospitals, however, every known language is encountered at one time or another. The custom obtaining in certain institutions of preparing translations into various tongues of the commoner questions essential to the obtaining of a history is not a wholly commendable one, in that the questioner limits himself to the questionnaire and thus often fails to obtain vital facts. In a great many cases relatives or friends who speak English accompany the patient and render the task easy. When an official interpreter is not at hand, one must avail oneself of the linguistic accomplishments of other patients.

The physician will often be surprised to find that histories obtained in the presence of relatives or friends differ radically from those volunteered when the examiner is alone with the patient. Experience and a natural talent for reading mental processes will in part suffice to determine whether or not the patient is "holding back"; as for the rest, inconsistencies in the history as first obtained and in the results of the clinical examination must serve to put one upon the right track. In venereal and sexual cases, particularly, it is advisable to postpone questioning until there is opportunity for private conversation.

The judgment of the physician must also determine when a history is likely to be inaccurate because of the physical condition of the patient. In many cases, although the patient is gravely ill, his answers will seem to indicate a clear sensorium. If the replies are satisfactory and dovetail properly, well and good; if not, recourse must be had to those about the sick person.

Tact and delicacy are prerequisites to an accurate anamnesis in many cases. By this is not meant a foolish reserve in asking necessary questions, but avoidance of that brusque, dictatorial manner which tends to place many individuals upon their guard and to make them actually secretive. It is a quite inexplicable frame of mind which prompts a person to consult a physician and then to conceal from the latter vital information; however, this is not at all infrequently the case. Although we must be gentle and sympathetic with patients of all types, whatever their symptoms may be, we need hardly say that these qualities are especially essential in the case of diseases of the sexual organs and in those involving the genitalia, for this seems to many individuals to be a field in which the physician is not entitled to know everything. It is in this field that the examiner can find full play for a tactful question, aimed

**DR. HOWARD A. SMITH
CHICAGO**

No.	Patient's No.:	Date:	Sex:	Age:	M.S.W.
	Name:		Color:	Nationality:	
	Residence:		Occupation:	Gain:	
			Height:	Weight:	Loss:
	Present Complaint:				Since:

Family History:	Father, l. health:	d. cause:	Brothers: l.	d.
	Mother, l. health:	d. cause:	Sisters: l.	d.
	Family tendencies:			

Previous Health: Childhood, adolescence; women (menstruation, pregnancies, miscarriages, pelvic infections); diseases (rheumatism, lues, gonorrhea, etc.); accidents, operations.

NAME	Habits—environment:	Bowel movements; work; wages; dwelling; bedroom; usual food; daily habits (work, rest, amusements, sleep); tea; coffee; tobacco; alcohol; drugs.
------	----------------------------	--

History of Present Illness: Duration; progress; onset; earliest symptoms; most troublesome symptoms; physical changes observed; former treatment.

General Inspection:	Appearance:	Temper-	Pulse:	Respiration:
	Development—nutrition:	ature:	Glands:	
			moist:	dry:
	Mouth—throat—teeth:	Eyes:	Skin: trauma:	scars:
			eruptions:	edema:

Diagnosis: Provisional:	Final:
--------------------------------	---------------

FIG. 3.—A FOUR-PAGE HISTORY FORM, WHICH, THOUGH RIGID IN SOME WAYS, POSSESSES MANY OF THE POINTS COMMENDED IN THE TEXT.

In the several subdivisions of history and examination, a reasonable amount of space is left for expansion, and the latter, with subsequent notes, can also be taken care of on the third page. The laboratory page is excellent.

GENERAL EXAMINATION

Digestive Tract:

Respiratory Tract:

Circulatory Tract:

Genito-urinary Tract:

Nervous System:

Date:

DETAILED HISTORY

LABORATORY REPORTS

Date at top of each column

URINE:	19	19	19	19	19
Quantity					
Appearance					
Reaction					
Specific Gravity					
Albumin					
Sugar					
Indican					
Sediment					
:					
BLOOD:	19	19	19	19	19
Hemoglobin					
Erythrocyte count					
Leukocyte count					
DIFFERENTIAL State No. Cells Counted					
Polymorphonuclear					
Lymphocytes					
Large mononuclears					
Transitionals					
Eosinophils					
Basophils					

SPECIAL LABORATORY EXAMINATIONS:

FIG. 3, PAGE 4.

here and there, with the result that all necessary information is soon at his disposal.

Of all the essentials to accuracy in history-writing, however, none is so important as a thorough analysis of the patient's symptoms, past and present. It is just here that the physician's skill and judgment are put to the severest test. To one man the symptom *pain in the stomach* means only that; to another who can analyze and correctly develop the facts bearing upon this manifestation, it means quite another thing—perhaps a tentative diagnosis. The term *chill* as given by the patient signifies relatively little unless an effort is made to bring out information as to its severity, duration, periodicity, etc. And *rheumatism*—there is surely no condition more frequently mentioned in the patient's recital or so often incorrectly named! Careful analysis should quickly demonstrate whether the pain is—or was—articular, muscular, or of another nature, whether it was associated with fever, whether it involved one or many joints, whether or not it was severe enough to confine the patient to his bed, whether or not it was associated with swelling and redness of certain joints and was accompanied by drenching perspiration, and so on. Rheumatism, unqualified, means little; rheumatism defined and properly qualified may determine the diagnosis.

This matter of the thorough analysis of all points in the patient's story applies with equal emphasis to all of its details—*present complaint, past illnesses*, etc. (see also p. 578). In many cases a history so taken and analyzed will enable one to make a highly probable diagnosis even before the examination is begun (pneumonia, duodenal ulcer, acute poliomyelitis, appendicitis, etc.); in all cases, it is a necessary prerequisite to an intelligent study of the patient as an individual.

MATERIALS

Before entering upon the subject of history-writing proper, it may be well to deviate from our principal theme for a moment in order to say a few words about suitable materials upon which to record histories and about commendable methods of preserving them. Although the recording and keeping of the hospital and dispensary histories should, in the main, follow the suggestions about to be made, the author's recommendations are intended especially for the needs of private practice.

Compactness, though axiomatic of modern business methods—and such have a distinct place in the keeping of medical history records—cannot be emphasized at the expense of serviceableness. The use of printed forms with definite space allotments for the items of the history and the physical and laboratory findings has already been sufficiently condemned. Cards or paper, blank except for captions such as name, date, occupation, address, place of birth, diagnosis, etc., are much less objectionable, as there is no restriction to the space which may be occupied by such features of the anamnesis and examination as may require expansion. The disadvantage in the use of any but very large cards (8x10 inches, or larger) is chiefly one of bulk, for as the record grows with

subsequent examinations of the patient and repeated laboratory tests, a rather unwieldy and space-consuming collection is the result. Another not entirely negligible objection to the use of cards is the matter of expense. Furthermore, when cards are employed, the tendency is to intermingle physical and laboratory data, a method which, as will be pointed out in detail later, detracts from serviceability in the matter of future reference. If, despite these disadvantages, cards are made use of they had better be of ordinary letterhead size ($8\frac{1}{2} \times 11$ inches) for reasons described below. The statistical information essential in every case—name, residence, age, occupation, etc.—may either be written at the top of the card in long hand or, better, printed just as in the case of the paper records about to be described. (For methods of filing cards and other types of records see page 567.)

For reasons which will appear, the author believes that a history sheet closely following that shown in Fig. 4 best fulfills the various demands made upon such forms. It consists, as will be noted, of four pages, the page size measuring $8\frac{1}{2} \times 11$ inches. The only printed items should be those above the horizontal line on the first page—which may, of course, be just as acceptably inserted in long hand—*Present Illness*, *Onset and Course*, just below the line on the same page, and *Laboratory* on the fourth page, which should be printed, as it serves to confine the laboratory data to this page. The other marginal captions: *Previous Illness*, *Habits and Routine*, *Family History*, *Venereal-menstrual Examination* and *Subsequent Data* are inserted in pen and ink where the demands of the history and examination place them.

Under the subhead *Examination* may be written in, if desired, the several phases of the examination, such as *General*, *Head and Neck*, *Pleura and Lungs*, *Heart and Vessels*, etc.; while under *Subsequent Data* are placed the dates on which later examinations are made. On the page devoted to *Laboratory*, the different forms of the latter—*Urinalysis*, *Blood*, *X-ray*, etc.—may be written in the margin, or rubber stamps may be employed for the purpose, a method which the writer finds very convenient and satisfactory. In either case the various groups of laboratory work should be so spaced—based with a reasonable degree of accuracy upon the particular type of case—as to allow ample room for subsequent examinations, the dates of the latter appearing in the margin beside the data.

Several modifications of the plan just described work out very well in practice. In the first place the history form may be made up of six pages instead of four, with the idea primarily of allowing sufficient space for the demands of practically every case. (In the four-page scheme additional pages of letterhead size may be inserted as needed.) Or the middle sheet of the six-page type may be reserved for laboratory data, thus providing for the latter two pages, instead of one. The middle, laboratory sheet—pages 3 and 4 of the six-page booklet—may be left blank except for the caption *Laboratory* at the top, and the ruled margins; or special forms for the examinations of a more routine nature may be printed thereon (Fig. 5). The objections to such printed forms

**DR. HOWARD A. SMITH
CHICAGO**

No.	Date	Referred by
Name	Address	
Occupation	Age	Place of Birth
Provisional Diagnosis		
Definitive Diagnosis and Outcome		

**Present Illness:
Onset and
Course**

**Previous
Illness:**

FIG. 4.—A FOUR PAGE TYPE OF CASE HISTORY FORM RECOMMENDED BY THE AUTHOR.

Habits and Routine:	
Family History:	
Venereal; Menstrual:	
Examination: (Various subheads of the examination may be inserted in this margin)	

FIG. 4, PAGE 2.

**Subsequent
Data:**

(Insert dates in
this margin.)

LABORATORY**Urinalysis**

Date_____ (Original)

(Place dates of later
examinations in this
margin.)**Blood**

Date.....

X-ray

Date.....

Stool

Date.....

are the same as those already directed against printed history and examination cards—they go far beyond the routine required for the average case and they are likely to prevent expansion when this becomes necessary. The particular case, for example, may demand twenty urinalyses to one hematologic examination, and yet a set form would allow about equal space for each.

Still another modification of the four-page form which has much in its favor is the use of special pages, of the same size ($8\frac{1}{2} \times 11$), for the different laboratory examinations, such pages to be fastened within the booklet by metal clasps. These additional pages should follow, in general, the forms shown in Fig. 5 and not those of the type of Figs. 6 and 7. For easy identification, different colors of paper may be used for the different laboratory examinations, but, in order to prevent undue bulkiness, two, or even three, subjects may be included on a single page, somewhat after the plan suggested in Fig. 5. The number of the history and the name of the patient appears at the top of each laboratory page; and each laboratory phase—*Urinalysis*, *Blood*, etc.—is properly labeled.

The number of these colored laboratory forms which may seem desirable will vary greatly; the physician in general practice will find two or possibly three such combination pages sufficient for all routine examinations. The specialist, on the contrary, will require forms suitable for particular purposes: field of vision, renal functional tests, diabetic charts, fractional gastric analyses and so forth; however, to attempt to reproduce, or even to discuss these various special forms is not within the scope of this work.

The letterhead size of page recommended in the various history forms and extra pages just described is preferable to other sizes not only because it affords sufficient space for nearly every purpose, but because correspondence relative to the case may be neatly and compactly filed away with it. The habit of stuffing cards and papers of various sizes in an envelope as a container for the records of each individual case detracts from system in the keeping of records. It is the author's custom to place five histories in a stout manila container, open at the top, and with a flap for the numbers of the records contained.

We come, finally, in the matter of materials, to methods of filing histories and of cross-indexing. Here again no attempt will be made to describe the many eminently satisfactory methods designed for this purpose. Any system which will readily enable the physician to find the particular history he wishes is satisfactory provided that, as the number of histories grows, the system does not become unwieldy. The alphabetical filing of records does become extremely unsatisfactory after a time, inasmuch as one finds it necessary to run through a certain number of histories, no matter how well subdivided the alphabet may be.

Distinctly preferable, in the author's opinion, is the numerical file. Reference to Fig. 4 will show that each anamnesis is numbered, the number on the history corresponding to a number on a card in a small card index system. The small card bears in addition the name of the

URINALYSES

[illegible]

BLOOD

DATE	Hb.	R.B.C.	C.I.	W.B.C.	STAINED PREPARATION							OTHER DATA
					NORMAL DATA				PATHOLOGIC DATA			
					Lympho.	Poly. N.	Poly. E.	Poly. B.	Large Mono. and Trans.	Red Cells and Platelets	White Cells — Red Cells	
												Parasites, Widal, Culture, Wassermann, etc.

FIG. 5A.

[illegible][illegible]

These forms contain relatively few of the objections mentioned in the text. The reverse side of the sheet on which all four forms are printed, may be used for other similar forms or may be left blank with the marginal caption: "Other Data; Special Data."

EXAMINATION OF BLOOD

RED BLOOD-CORPUSCLES—

No. per cu.mm.....	How estimated.....
Poikilocytes.....	Normoblasts.....
Megalocytes.....	Megaloblasts.....
Microcytes.....	Microblasts.....
Granular degeneration.....	Polychromatophilia.....

LEUKOCYTES—

No. per cu.mm.....	
Differential count.....	
Lymphocytes.....	per cent.
Large Mononuclear and Trans.....	"
Polymorphonuclear Neutrophils.....	"
" Eosinophils.....	"
" Basophils.....	"
Neutrophilic Myelocytes.....	"
Eosinophilic ".....	"
Stimulation forms.....	"
Undetermined.....	"

Hemoglobin.....	per cent.	Instrument.....
Specific gravity.....	(.....%	Hb. Hammerschlag table)
Color index.....	Volume index.....	
Coagulation time.....	Blood platelets.....	
Blood Cultures (Media.....)		
Animal Parasites.....		
Serum reactions.....		
Miscellaneous.....		

FIG. 6.—AN UNSUITABLE FORM FOR RECORDING BLOOD EXAMINATIONS.

There are repeated examinations of the blood in a given case, and, as each sheet can be used for only one examination, there will be a consequent bulky accumulation of such sheets and comparison of the records of different dates will be difficult. (See the forms shown in Fig. 5.)

EXAMINATION OF URINE

ROUTINE COMPLETE EXAMINATION

Sp. gr. Reaction

Color Quantity $\left\{ \begin{array}{l} \text{Single} \text{} \\ \text{24 hrs.} \text{} \end{array} \right.$ Consistency

Sediment Cloudy Odor

Albumin Sugar

Acetone Diacetic Acid

Casts R. b. c.

W. b. c. Other Cells

Crystals Amorphous

Miscellaneous

SPECIAL QUALITATIVE EXAMINATIONS

Mucin Bile Indican Hb

Diazo Glycuronates Cammidge

Drugs Miscellaneous

Other reducing substances Other Albuminous bodies

Bacteriologic

SPECIAL QUANTITATIVE EXAMINATIONS

Sugar (kind Test Sol.) per cent.

Albumin (Method) per cent.

Total solids (..... coefficient) gms. per liter

Total N (Kjeldahl) gms. in 24 hrs. Ammonia (NH_3) gms. 24 hrs.

Urea (..... Method) gms. in 24 hrs. $\frac{\text{N} - \text{NH}_3}{\text{Total N}} =$

Uric Acid (..... Method) gms. in 24 hrs.

Other nitrogenous bodies (..... Method) gms. in 24 hrs.

Acetone (..... Method) gms. in 24 hrs.

Phosphates (..... Method) gms. in 24 hrs.

Chlorids (..... Method) gms. in 24 hrs.

Sulphates (..... Method) gms. in 24 hrs.

FIG. 7.—AN UNSUITABLE FORM FOR RECORDING URINALYSIS.
(See note in explanation of Fig. 6.)

patient and either the diagnosis in the case—for a quick study of records—or ledger rulings for that phase of practice. The ideal containers for histories and card indices are the metal files with drawers of the necessary sizes, as a safeguard against loss by fire.

THE HISTORY PROPER

Mention was made on an earlier page of the necessity of employing some skeletal outline in the writing of the history proper, upon which the individualizing details of the particular patient's story should be built. These main divisions, which are more or less stereotyped and appear under one name or another, with some variation in sequence, as a part of practically every history, are the following:

- (1) Present illness.
- (2) Previous illness.
- (3) Family history.
- (4) Patient's daily routine; frequently called habits, or personal history.
- (5) Venereal history. This appears to better advantage, perhaps, as a special subhead than as part of previous illness.
- (6) Menstrual history in the case of women.

Present Illness.—While the history is being written the patient should sit, or lie, facing a good, although not intense, light in order that the physician may study the sick man's facial expressions, and, generally, his manner of telling his story. To the observant, and especially to the experienced examiner, a considerable amount of information is given in this way, as regards the reliability and weight of the statements made and in general as to the mental makeup of the patient. The trained and attentive ear and eye, unaided by instruments, note a wealth of diagnostic material, some of the details of which are mentioned in section 4 of this chapter (page 587).

In the matter of developing the *present complaint*, as in the case of practically all other subdivisions of the history, there is a considerable choice of method. Although half a dozen or more satisfactory forms of procedure might be mentioned, the author will, to avoid confusion, confine himself to a discussion of two only. Later on, with a growing experience, the practitioner will very probably evolve a method more satisfactory for his purposes than are those offered here; however, at first, it is advisable that this experience be gained along one or the other of the two lines to be mentioned.

In the first method of developing the present complaint, each symptom as it is given is taken down and analyzed—the explanation of this term will be considered at length a little later (page 576)—from its onset to the time when the patient presents himself. A slight variation of this method is to enumerate the list of symptoms at the beginning, following which each complaint is considered in detail (Fig. 8).

In the second method—the one especially recommended by the author

DR. HOWARD A. SMITH
CHICAGO

No. 642 Date 8/24/16 Referred by _____

Name Williams, George Address 1011 A Street, Chicago

Occupation Bond Salesman Age 25 Place of Birth Chicago

Provisional Diagnosis Typhoid Fever

Definitive Diagnosis and Outcome Typhoid Fever; Myocardial Degeneration.
Recovery (Complete?), 2/18/17.

**Present Illness:
Onset and
Course**

This began about ten days ago, there has been no previous illness of a similar nature.

RÉSUMÉ OF SYMPTATOLOGY SINCE ONSET OF TROUBLE:

Headache
Cough
Loss of Appetite
Weakness
Disinclination to work
Fever
Constipation
Nosebleed
Abdominal Pain

SYMPTOMS IN DETAIL:

Headache:--This was one of the earliest symptoms noted and is still present, although not so severe. The patient has never been troubled with headache in the past. The pain is chiefly frontal and is present more or less throughout the day except for brief intervals after taking aspirin. Pressure does not aggravate the discomfort; heat relieves it somewhat.

Cough:--The patient began to cough soon after the headache appeared, and has coughed more or less constantly throughout the day since. In the last few days there has been some improvement. Small amounts of thin, whitish sputum; no blood.

Loss of Appetite:--There has been little inclination to eat since the very onset; no kind of food is tempting. No symptoms on the part of the stomach.

**Previous
Illness:**

FIG. 8.—ILLUSTRATION OF THE FIRST METHOD OF DEVELOPING THE "PRESENT ILLNESS" OF THE PATIENT.

The résumé at the beginning may be omitted, but is recommended for quick orientation.

—the patient's complaint is considered under the following subdivisions:

(1) *The onset* of the trouble, including the duration of the latter, its earliest manifestations and a résumé of any previous attacks.

(2) *The course* of the illness since its onset (most recent exacerbation if there have been previous attacks; the latter are considered under 1).

(3) *The present status* of the process, representing the condition of the patient when he presents himself for examination (Fig. 9.)

The plan just considered has the advantage over the first of placing symptoms side by side in their time relationship. In the first plan, a certain loss of perspective is bound to occur because of the seriatim analysis of each symptom from beginning to end.

The ideal method in the preparation of a case history is to take notes as the information is gathered and then to write the history in its final form. This plan makes for coherence, compactness and a logical arrangement. With a growing experience, however, the physician does not find it unduly difficult to write a good history as he questions the patient; and for the busy man who takes his own histories, this is the only practical method. Nevertheless, the best of men will find, despite due care in the gathering of symptoms, that it will be necessary not infrequently to "fill in" one or more places in the patient's recital—this applies not only to the present complaint, but also to the other subdivisions of the history—because of further questioning called for by facts brought out either in subsequent parts of the anamnesis or in the examination of the patient.

At this point it seems advisable to consider in some detail features which concern all subdivisions of the history proper but more particularly, perhaps, the substance of the present complaint. The author refers to the matter of *the correctness of the replies made by the patient to our inquiries* and to *the analysis of the symptoms* given by him. In questioning the accuracy of his replies, no reflection is necessarily cast upon his veracity. Misleading answers, as the experienced physician knows, are due to several factors among which are the carrying about by the patients themselves of careless or inaccurate diagnoses made by former physicians, medical advice given by non-medical friends, the reading by the patient of "quack" advertisements, and ignorance. Untruthfulness does, of course, at times enter in as a factor.

No term is perhaps so loosely employed by the patient as is *rheumatism*, which is used to cover such dissimilar conditions as tuberculosis of bones and joints, the lightning pains of *tabes dorsalis*, true rheumatic fever, trichinosis, gout and other pathological conditions almost too numerous to mention.

Malaria is another much abused diagnostic term. By carefully placed questions as to the place of residence at, or shortly before, the onset of the trouble, as to the duration, the treatment (quinin), etc., one is enabled to differentiate between this and other conditions with regularly recurring febrile manifestations.

The *neuritis* of the patient is seldom neuritis, being more commonly a subdeltoid bursitis, a *tabes*, a cervical rib or what not. And what

DR. HOWARD A. SMITH
CHICAGO

No. 642 Date 8/24/16 Referred by _____

Name Williams, George Address 1011 A Street, Chicago

Occupation Bond Salesman Age 25 Place of Birth Chicago

Provisional Diagnosis Typhoid Fever

Definitive Diagnosis and Outcome Typhoid Fever; Myocardial Degeneration.

Recovery (Complete?), 2/18/17;

Present Illness:
Onset and
Course

ONSET.--The present complaint--no previous similar trouble--began about ten days ago with headache, cough, loss of appetite and nosebleed. The headache, which was probably the first symptom noted, was very severe, the more so as the patient has never suffered from it in the past. The pain was chiefly frontal in location, and has been present more or less throughout the day except for brief intervals after taking aspirin. Pressure did not aggravate the discomfort; heat relieved it somewhat. The cough began soon after the headache appeared and has been present practically throughout the day. There has been a small amount of thin, whitish sputum, but no blood. Loss of appetite came on early and has applied to all kinds of food. There have been no other symptoms on the part of the stomach. The patient has had no actual nosebleed, but has noticed streaks of blood on his handkerchief on several occasions after blowing his nose.

COURSE.--In the ten days since the onset, the headache has continued severe until a few days ago, when it began to abate. The same has been true of the cough. Anorexia has persisted. There has been no epistaxis after the first few days. In addition, since the onset, the patient has noticed an increasing physical weakness with inability to concentrate on his work. It has been necessary, also, to employ enemata to obtain a bowel movement, although the patient was always regular in this respect. In the last day or two there has been what appears to be actual pain in the right lower quadrant of the abdomen, there has been no vomiting. The patient has felt feverish for the last week, and his temperature yesterday was found to be 103° F

Previous
Illness:

PRESENT STATUS.--The increasing weakness has forced the patient to take to his bed. He says that he is satisfied just to be left alone. Aside from feeling very hot, drowsy, and uncomfortable, and being strongly averse to the sight and mention of food, he makes little complaint.

FIG. 9.—THE SAME CASE HISTORY AS IN FIG. 8, ARRANGED ACCORDING TO THE SECOND METHOD OF DEVELOPING THE "PRESENT ILLNESS."

was diagnosed for one reason or another as sciatica proves to have been, or to be, sacro-iliac disease, hip-joint disease, flat-foot or some other condition.

Pain in the stomach, when analyzed, may prove to be appendicitis, renal or biliary colic or one of the many other acute abdominal disturbances associated with pain.

Many patients describe *fever* as a symptom of the onset of their illness. Inquiry, however, very frequently shows that the individual did not use a thermometer, but merely felt feverish, while the course of the disease indicates that an elevation of temperature was probably at no time present. The same is true of *chill*; patients generally confuse a chilly sensation, such as occurs frequently at the onset of many acute infections, with a true rigor, as in malaria and pneumonia, in which the individual shakes the bed in the paroxysm and finds it difficult or impossible to get warm.

Pain in general is loosely employed to designate a great number of unpleasant sensations. Careful inquiry will usually elicit the nature of the "pain"—whether it consisted in a feeling of pressure, or of weight, in a burning sensation, a tired feeling or an actual pain—a differentiation which is of extreme importance, for example in the diagnosis of gastric conditions.

Finally, as another illustration of the patient's incorrect use of medical terms, one might mention the ill-defined employment of the word *stomach*, which to the layman may mean anything from the diaphragm to the pelvic floor.

Examples of incorrect usage of medical terms by the patient might be multiplied almost indefinitely. Those given, however, are fairly illustrative and should serve as a warning to the beginner not to accept at face value the greater number of the patient's anamnestic statements.

No single feature of history writing is as important, perhaps, as what has been termed *the analysis of symptoms* given by the patient. No history can properly be called such unless the factors qualifying each complaint are fully amplified and arranged to throw the greatest amount of light upon the symptom in question. In putting questions designed to bring out these qualifying details, the knowledge of pathological complexes has an unlimited field, and, as has already been mentioned, the medical training and experience of the examiner may be fairly judged by the extent to which he rounds out the setting of the important symptoms.

The physician must, at first, learn to ask questions which are based not upon clinical experience alone, but obviously essential, one might say, even to the intelligent layman. If a patient complains of *loss of weight*, it is natural to ask him how great the loss has been, over how long a period the weight has been declining, whether the loss has been constant or has been arrested by temporary gains, whether change of clothing or the use of different scales from time to time may not have been factors, whether a change in work or working hours has taken

place coincidently with the falling off in weight, and so on. Later, with each year of added clinical experience, questions based upon a knowledge of conditions associated with a loss of weight can be added, questions, for example, calculated to indicate the possibility of the causative factor being tuberculosis, Graves' disease, malignancy, diabetes, etc.

The following illustrations will serve to give the reader an idea of what the author considers to be an analysis of symptoms.

Symptom—Pain in the Stomach:

Analyzing Questionnaire:

- (1) Where is the pain, in the stomach or the region of stomach, distinctly to the right of the median line (duodenum, gall-bladder), over the appendix, substernal or elsewhere? Answers seem to indicate that the pain originates in the gastric region.
- (2) Is the complaint actually one of pain (like that due to toothache, a bump on the shin, a blow on the nose) or does inquiry show it to be a burning sensation, a feeling of pressure or weight, a grinding sensation, a feeling of emptiness, or even nausea? If pain is present is it colicky, boring, dull, sharp or pulling? Some observers regard an actual pain as highly suggestive of an organic gastric disorder, as contrasted with one of a functional nature.
- (3) How long has the pain been present, and has it been constant or periodic since its onset?
- (4) Is the pain present throughout the day, or is it dependent upon some particular event of the day, such as mealtime, or the period before meals, or late at night?
- (5) If the pain is related to the taking of food, how long after eating does it appear?
- (6) Does the pain depend upon the kind of food taken, following, for example, the ingestion of coarse foods and not of soft or liquid kinds, or occurring after the ingestion of very hot or very cold articles, but not after those of a moderate temperature?
- (7) Is the pain relieved by the taking of food and, if so, by what types of food?
- (8) If vomiting is an associated symptom, is the pain relieved thereby?
- (9) Is the position of the pain constant, or does it radiate, and, if so, in what direction?
- (10) Does change of bodily position have an effect upon the occurrence or the severity of the pain?
- (11) Does bicarbonate of soda relieve the pain?

The above list of questions by no means exhausts the analysis of *pain in the stomach*. However, enough information may be obtained by
VOL. I.—37.

the answers to this partial list to determine with a fair degree of accuracy: (1) whether or not the sensation complained of is actually a pain, (2) whether or not the location is gastric (or in the neighborhood of the stomach), (3) whether in connection with other features of the anamnesis—age, character of vomiting, loss of weight, etc.—a benign ulcer of the stomach is suggested, and its probable location, and (4) whether a duodenal ulcer is likely—late pain, night pain.

Analytical questioning such as the foregoing emphasizes very forcibly a point to which attention has already been directed, namely, that the fuller the experience of the examiner, the more profitably he can elaborate the various symptoms constituting the patient's complaint.

Symptom—Swelling of the Ankles:

Analyzing Questionnaire:

- (1) Has the trouble been present before, and, if so, for how long, and how completely and under what treatment did it disappear?
- (2) If present before, was it more or less severe than at present?
- (3) Is the swelling constant, or does it disappear or recede, and when—mornings or evenings?
- (4) Has the amount of urine, or the frequency of urination, altered coincidently with the appearance of the swelling?
- (5) If fluid is also present in the abdomen, did the ascites precede or follow the ankle edema?
- (6) Is the swelling painful or red?
- (7) Is the edema unilateral, slightly or predominantly so, or bilateral?

The answers to these questions, especially when combined with information derived from associated symptoms (shortness of breath, vomiting of blood, hemorrhoids, headache, etc.) and from details of the previous illnesses (rheumatism, tonsillitis, etc.), and also from such etiological factors as alcohol, will serve to orient the examiner, to some extent, as to whether he is dealing with a general process, such as a renal or cardiac affair, a cirrhosis of the liver, or with some local condition, such as varicose veins or thrombophlebitis.

It is hardly necessary to illustrate further the manner of analyzing symptoms. In all, the method involved is the same, and while a finished analysis demands an extensive experience and a mature judgment, the young physician, by applying the principles involved, can elaborate a creditable and diagnostically helpful picture.

Previous Illness.—As already pointed out, what has been said concerning the accuracy of the patient's statements and the analysis of his symptoms is fully as applicable to diseases and symptoms which have existed in the past as to the details of his present illness. Also, from the point of view of form and coherence, it is probably advisable to exclude from the subdivision of the anamnesis under consideration

a description of previous attacks of the same illness which brings the patient to a physician, inasmuch as this belongs logically to the present complaint. Furthermore, it is a matter of custom, and promotes clarity, to consider past illnesses referable to the venereal tract and the menstrual function under separate captions (*see* below).

Experience shows that a worth while account of the patient's previous sicknesses is most likely to be obtained by asking him specific questions along set lines. To do this it is necessary to learn what conditions are apt to have sequelæ. The following are the most important, together with their more common complications:

- (1) Rheumatic fever (endo-, peri-, myocarditis).
- (2) Tonsillitis (cardiac and renal pathology; secondary focal processes, such as iritis, "rheumatoid arthritis," osteomyelitis, etc., etc.).
- (3) Typhoid fever (gall-bladder disease; osteomyelitis; myocardial degeneration).
- (4) Scarlet fever (nephritis, middle ear disease and its complications).
- (5) Whooping-cough and measles (tuberculosis).
- (6) Pleurisy (tuberculosis). It is advisable to inquire as to the occurrence of pleurisy, pneumonia and "diseases of the chest" in general, for the light they may throw upon the thoracic findings later revealed by the examination, even though these findings may have no bearing upon the present illness.
- (7) Infections in general (cardiac and renal pathology).
- (8) Influenza—a waste-basket of disease called "grippe" by the patient (cardiac and renal pathology; chronic ill-health).

The above list of conditions is perhaps sufficiently inclusive as a routine; it does not, of course, embrace all diseases which may at one time or another have an etiological bearing upon the present illness of the patient. The individual case frequently requires an extra-routine line of questioning. For example, in the case of a patient whose complaint is suggestive of a carcinoma of the stomach, it would be indicated to inquire specifically as to the occurrence in earlier years of a symptom-picture permitting the presumptive diagnosis of gastric ulcer, of which the patient had remembered only a few hazy details catalogued in his mind as "indigestion." Or, if the present complaint and findings speak for an hepatic or subphrenic abscess, it would be highly important to discover that at an earlier period there had been symptoms which at the time made little impression upon the patient but which analysis shows to have been manifestations of appendicitis (called "stomach-ache or dyspepsia) or of a dysentery (described as diarrhea).

In addition to specific inquiry as to the diseases enumerated above, and questioning along less routine lines as dictated by other phases of

the anamnesis and by the examination of the patient, it is also advisable to question the patient concerning symptoms which may have been noted at an earlier day. In sharp contrast to those individuals who consult a physician at the very inception of a symptom are those—and their number is not small—who overlook and forget manifestations which are not serious enough to compel them to take to their beds.

Among the more important of such past symptoms of disease, which should form a part of the routine questionnaire and be analyzed as are the symptoms of the present complaint, are the following:

- (1) Headache.
- (2) Swelling of the ankles.
- (3) Cough.
- (4) Expectoration of blood.
- (5) Vomiting and vomiting of blood.
- (6) Anomalies of urination and of the urine.
- (7) Shortness of breath.
- (8) Pain in the chest.
- (9) Pain in the abdomen.
- (10) Constipation and diarrhea.
- (11) Marked changes in weight.
- (12) Jaundice.

It is not within the province of this volume to discuss the diagnostic data which may be obtained from inquiries directed along these lines; their value becomes increasingly evident with the medical progress of the student.

The patient is questioned, finally, as to *trauma* and *operation*. In many cases, when the relation of one or the other of these factors to the present illness is self-evident, the patient has already mentioned them. In the case of slight trauma, however, it is often difficult or impossible to obtain a history of its occurrence, even though the picture strongly suggests it (sarcoma, bone tuberculosis). The details of a previous operation may throw light upon a condition in one of two ways: they may either account etiologically for the present illness (post-operative infection, adhesions, lung abscess following tonsillectomy) or, when the work has been done and recorded by a competent pathologist, they may explain the manifestations which have brought the patient to the physician. For instance, a former operation revealed a hypernephroma which has given rise to the present multiple bone changes; or, at operation for suspected peptic ulcer, the abdominal contents were found to be normal, in view of which the present (recurrent) gastric disturbances are probably functional.

The relationship of injury to the present illness may be obvious (fracture, rupture of the bladder, etc.) or it may be highly probable (Jacksonian epilepsy due to injury to the head rather than to brain tumor, sarcoma of an extremity following a single trauma). Trauma also opens up the wide domain of neurasthenic and hysterical conditions in which

the examiner is put upon his mettle to detect malingering in its bearing upon personal injury law-suits.

Family History.—While almost general unanimity exists as to the “hereditary” tendency of certain diseases, there is a considerable diversity of opinion as to whether or not a number of other conditions run in families. Two processes in particular must always be specifically searched for, namely tuberculosis and cancer. This is not the place to discuss the genuinely hereditary nature of the former; suffice it to say that actual transmission via the sperm, the ovum or even the placenta is extremely rare. In the last analysis, *tuberculosis is largely a disease of propinquity*. The disease tuberculosis, furthermore, must be sharply distinguished from tuberculous infection. The evidence is all in favor of the view that between the ages of six months and fourteen years practically all of us are infected by tubercle bacilli; however, the great majority of us, fortunately for the human race, are able, for one reason or another, to check the process clinically. A minority, not endowed with efficient protective forces, succumb during that early period to the disease tuberculosis.

After this preliminary infection, a number of factors determine whether or not the infection will be lighted up into active disease. The individual born without a family taint will not, under ordinary conditions, contract tuberculosis, even though he is exposed to an open case for a long period. The same individual will probably not be affected by such predisposing diseases as whooping-cough and measles. If he is an alcoholic, however, or in a non-resistant state from other causes—diabetes, malnutrition, etc.—any natural immunity he may have may be canceled. In other words, in the case of the individual with little or no tuberculosis in his family history, unless certain very pronounced predisposing factors be present, tuberculosis is relatively little to be feared, even though the element of exposure to open cases is at hand. This is one phase of the matter of the family history in its relation to the question of tuberculosis.

In the case of the individual from a tuberculous family, however, things are quite different. His constitutional makeup is such that exposure to open cases is positively dangerous, and pertussis and measles are real menaces. A big factor in the two types of individuals is, naturally, that the one must go out of his way, so to speak, to expose himself to the tubercle bacillus, while the other is born and raised in its presence.

All of these various factors must be taken into consideration when the patient is questioned in regard to tuberculosis. If there is no family history of the disease the chances are that the present complaint is not tuberculosis unless one of the above-mentioned predisposing conditions is present. An alcoholic from a family in which there has never been a case of tuberculosis is as likely to contract the disease as is a non-alcoholic who is constitutionally predisposed and has remained in his infected milieu. Another point of importance is the length of time during which an individual with a “bad” history has remained in the infected surroundings. For example, even if both parents and several

brothers or sisters have succumbed to the disease, provided the patient himself was taken at an early age from his unhealthy environment and has followed a careful, hygienic routine, his chances of having escaped without mark may be considered excellent.

The foregoing remarks are by no means without exception and have been made solely for the purpose of showing, first, how little real information is to be gained merely by asking the patient whether or not there has been tuberculosis in his family, and, second, how many and how varied the conditions are which predispose an individual to the disease.

In the case of cancer, the situation is quite different. The tendency of carcinoma to run in families is generally recognized and must always be assigned due importance in the taking of the history.

There is a considerable difference of opinion as to whether or not the predisposition to a number of other conditions is handed down from one generation to the next. Some observers insist that the interrelated complex of contracted kidney, arteriosclerosis, and arterial hypertension manifests a disposition to reappear in certain families; others that cardiopathies show a similar disposition. However, our ever increasing knowledge of the infectious nature of this latter group would seem to render this theory rather hazardous, unless we assume that the members of certain families inherit cardiac structures especially susceptible to infection. Perhaps even less definite is the matter of gout in this regard. Thus, in spite of the fact that in somewhat over one-half of the cases parents or grandparents have been affected, it is difficult to say whether a uratic disposition has been inherited or whether the son eats and drinks as did his father and grandfather.

There are two conditions in which the hereditary factor is very pronounced but which scarcely require investigation in the average case. These two diseases are hemophilia and insanity. We must inquire as to the former particularly before subjecting a patient to a surgical operation. In the insanities, heredity plays a very great rôle, and the history of a family predisposition may be of considerable help in the diagnosis.

Diabetes also exhibits a marked hereditary tendency, and although such a history may have little diagnostic value, it should be sifted in the glycosuric individual, from the point of view of statistical interest.

In certain diseases of the nervous system, finally, the family or hereditary factor may be of variable importance. Epilepsy, although probably not an inheritable affection in the great majority of cases, unquestionably occurs with great frequency in families of neurotic taint (hysteria, insanity). Chronic alcoholism in the parents also plays an important part in the production of, or predisposition to, epilepsy in the offspring. Affections of the motor tract, especially progressive neural muscular atrophy and the muscular dystrophies, are frequently familial; hereditary spastic paraplegia and hereditary ataxia (Friedreich's ataxia) tend to be familial rather than hereditary conditions. Syringomyelia is occasionally a family disease; amaurotic family idiocy (Sach's disease) is characteristically so.

Personal Routine (*Habits; Personal History*).—The term *personal routine* is suggested in preference to the more commonly employed *personal history* or *habits*, because it more nearly describes the data included under this caption of the anamnesis. One or more of the points about to be discussed may have been fully analyzed in connection with the Present Complaint; in this case, repetition under the heading of Personal Routine will of course be unnecessary.

Each patient should be questioned specifically in regard to the following items:

OCCUPATION.—It is not enough that the individual's occupation be noted at the beginning of the history; he must be questioned also as to the details of the conditions under which he works. These details include his working hours, the amount of time he allows himself between arising and beginning work, the time he takes or is allowed for luncheon, the conditions as to light and ventilation under which he works, and his personal feeling toward his work. In occupations, furthermore, which have a special etiological bearing upon certain diseases—lead industries, for example—the patient must be asked concerning the precautions which the employer recommends to prevent lead-poisoning. Even excepting the so-called occupational diseases—those due to the various trades in which lead is used, as in the case of caisson workers, workers in phosphorus, etc.—the interrelationship of occupation and disease is in many cases very close. The subject is so large that a knowledge of its details must be gathered with the student's growing experience. As illustrations may be cited: tuberculosis in carpenters, gout in bartenders, scurvy in cooks, myocardial degeneration in individuals who are constantly exposed to extreme temperatures (locomotive firemen and engineers), or to sudden changes in temperature (packing-house employees).

DIET.—The degree of detail with which this feature of the history is to be analyzed will depend entirely upon the nature of the complaint. In a case of pernicious anemia or ulcerative endocarditis, for example, the habits of the patient as to eating will scarcely add any information of importance. In diseases of the gastro-intestinal tract, on the contrary, the matter of the diet must be taken up in fullest detail. Inquiry must be made as to the number of meals eaten per day, the regularity of the meals, the quantity of food ingested, the general character of the diet, the peculiarities of the patient as regards very hot or very cold foods, highly seasoned dishes and foods which are particularly indigestible (pickles, cucumbers, hot breads, fried articles of diet), late dinners, banquets, etc. All of these items must be considered in relation to the particular complaints of the individual.

Many conditions require questioning along special lines in the matter of diet. In *angina pectoris*, for instance, it is important to learn whether the patient is in the habit of eating his heaviest meal at night, and whether he is given to indulgence in foods which tend to produce abdominal distention. In cases suggestive of *alimentary glycosuria*, the question of the amount of carbohydrates ingested is of prime importance. It is not difficult to understand why the patient whose diet consists

chiefly of rye bread, herring and coffee may present himself with a well-developed case of scurvy, nor why the man who eats foods which leave practically no residue—eggs, meat, bread—and especially one who is a dainty eater, is likely to be troubled with *constipation*.

The author has merely touched the surface of this very large and important subject. The quantity, and especially the quality, of the food have a very intimate bearing upon many disease processes. Some, indeed, for example beriberi and pellagra, are in all probability due to dietetic errors.

BOWELS.—The average normal individual has one complete evacuation of the bowels daily. However, there are exceptions to this rule which may nevertheless be regarded as normal. One man, for example, may remain in good health with a movement every second day; another with two moderately large movements daily.

The examiner must not be satisfied with the answer that the patient has a daily evacuation. He must ask also as to the size of the stool, and its character—whether it is normally formed, soft, mushy, hard and ball-like, etc. The analysis of the present complaint should have brought out such facts as tar-like stools, colorless stools, the passage of large amounts of mucus, painful defecation and the like.

Finally, it is well to ask in every case as to the use of cathartics—the kind, the frequency of use and the length of time during which they have been necessary.

ALCOHOL.—There should be no reserve in obtaining the facts as to the use of alcoholic beverages. Aside from the general importance of this subject, there are several special points which must be included in the questionnaire. In the first place, patients not infrequently say that they do not drink alcoholic beverages. Upon further questioning, however, they admit that they have not used alcohol for such and such a period—the beginning of the latter coinciding rather closely with the onset of their symptoms—but that previously they drank more or less excessively. Again, one not infrequently discovers that although the patient is not an alcoholic in the ordinary sense of the word, he has been addicted for a variable period to the use of certain patent medicines, the alcoholic content of which may be anything but negligible. Finally, information must be obtained as to the usual daily quantity of alcohol taken, its quality (if whisky), its nature (beer, wine, whisky, absinthe), and as to whether the drinking has been steady or periodic.

EXERCISE AND RECREATION.—Although the saying “All work and no play makes Jack a dull boy” is old and threadbare, the truth it contains is always fresh. Other things being equal, the man who takes his outdoor exercise and vacation regularly is most likely to remain well. This has been demonstrated especially by the popularizing in recent years of golf. The man—and the woman—above forty who had previously begun to feel old and to need the services of a physician more and more frequently, has found something of what Ponce de Leon went so far to find.

It is an almost everyday experience for the physician to see a case

which requires nothing so much as a change of surroundings or more exercise in the open. And this is neither the need nor the prerogative of the rich man alone.

DRUGS.—As in the case of alcohol, so with drugs, the physician should exercise no foolish reserve in putting direct questions. In many cases, mere observation of the patient—his approach, his speech, etc.—tells the whole story, rendering questions almost unnecessary. Opium, and its many derivatives, and cocain, are in the great majority of instances the drugs employed, in the sense of drug addiction. Morbid conditions may, however, not infrequently be traced to the regular use, even in moderation, of such substances as aspirin, antipyrin, acetanilid, etc.

SLEEP.—There is no hard and fast rule as to the time the average normal person requires for sleep. Eight hours may be regarded as sufficient for the majority of mature individuals. However, some require nine hours or even more to feel "fit," and others are satisfied with six or less. In many, if not most, cases as an individual gets along in years he finds that he needs much less sleep than the young adult. Also, toward middle life, many persons find that they have acquired the habit of awaking very early in the morning and that they are ready to begin the day's work, irrespective of the hour at which they may have retired the night before.

Bearing these facts in mind, the examiner should inquire into the patient's sleeping régime—how long and how well he sleeps, and whether he awakens refreshed. One should inquire, finally, as to the conditions of temperature and ventilation under which the patient sleeps.

TEETH.—In view of the established importance of the condition of the teeth in the state of the patient's health, questions bearing upon the daily care of the teeth and the regularity with which the individual consults his dentist should form part of the routine in every case.

TOBACCO.—This item should be as carefully investigated as is the subject of alcohol, because of the many injurious effects of smoking upon the predisposed individual. Conditions of vascular spasm (angina pectoris, intermittent claudication), gastric disorders, insomnia, nervous disorders, involvement of the optic nerve and cardiac irregularities are a few of the more important disturbances more or less directly attributable to the use of tobacco in excess or to the use of tobacco in any amount by hypersusceptible individuals.

OTHER FACTORS.—Finally, in certain cases, it becomes necessary to go into the matter of the patient's clothing, his sexual habits, his business or family worries and other details of his routine life.

Venereal History.—Syphilis and gonorrhea are the two venereal diseases concerning which specific questions are to be put. Different courses must be pursued, depending upon the sex of the patient. A man will as a rule admit readily enough that he has had one or more attacks of gonorrhea, especially if it be spoken of as "clap." It is more difficult, as a rule, to obtain a history of syphilis. This is not so much a matter of concealment on the part of the patients, who fortunately have learned much through the medical propaganda of recent years

concerning the by-products of the disease, and are generally willing and even eager to give the physician all the information they can. It is rather due to ignorance either of the meaning of the term or of the fact that they have been infected.

It happens not at all infrequently, for example, that the chancre was intra-urethral and associated with a neisserian infection, and that the secondary manifestations were transient or practically absent. Many patients are perfectly honest and correct in their statements that they have never observed cutaneous manifestations; others have seen no reason to distinguish between a syphilitic sore-throat and other anginas which they may have had from time to time. Extragenital chancres, and especially syphilis insontium, very frequently remain unrecognized.

The venereal history of the married male also includes information as to the health of the patient's children and as to any miscarriages which his wife may have had.

Syphilis is widespread and its sequelæ are extremely important. It is therefore fortunate that the case upon which the history throws an inadequate etiological light can be illuminated in still other ways. The author refers to the several laboratory methods of the last decade, namely the Wassermann reaction in the blood and in the spinal fluid—with a provocative salvarsan injection, if necessary—the luetin cutaneous reaction, and the study of the cerebrospinal fluid.

In the case of women patients direct questions as to syphilis and gonorrhea are generally omitted. Circumlocution is usually satisfactory. Thus, if the present complaint, reinforced by the local examination, indicates a salpingitis, the patient may be questioned as to a previous vaginal discharge—its color, thickness, duration, effect on the act of urination, etc. If syphilis is suggested by the history already taken, she may be questioned as to the occurrence of sore throat, exanthem, loss of hair, headache and other manifestations of the secondary period. A woman rarely has knowledge of the primary lesion. The most important information, however, is obtained from the menstrual history, which includes questions concerning miscarriages (*see* p. 587). Finally, as in the case of the male, if all of these leads yield nothing, the laboratory is the decisive recourse.

Menstrual History.—In the case of patients presenting themselves with a distinctly gynecologic complaint, the present and past details (including operations) bearing upon that complaint should be analyzed under the subdivision: Present Complaint (p. 572); in the remainder of the cases, all illnesses of pelvic origin are to be considered in the subdivision under discussion.

The following questionnaire applies to the menstrual function:

(1) The age at which the monthly periods began, the time which elapsed before the menses became regular, and the symptoms, if any, which marked the period of adolescence.

(2) The type of menstruation, i.e., twenty-eight-day type, thirty-day type, etc.

- (3) The regularity of the menstrual flow.
- (4) The amount of flow.
- (5) The duration of flow.
- (6) The symptoms present during the period.
- (7) If the climacteric has taken place, the age at which it occurred, the symptoms of the transition, and the manifestations, if any, which have appeared since the change.
- (8) The number of children born, if any, their ages and state of health; the number of children who may have died and the causes of their death; the number of miscarriages and their time relation to full term deliveries.

As has already been stated, important light as regards syphilis in the patient's anamnesis is thrown by the history of miscarriages. Following marriage, if one pregnancy after another results in a miscarriage, each of which occurs at a time somewhat later than its predecessor, one child being delivered dead at term and the next living only a short time, the evidence is practically complete that the mother has syphilis. Less marked variations of this sequence possess a significance only less important. One or more miscarriages scattered irregularly among full term deliveries of children who have survived and remained healthy have relatively little significance, so far as lues is concerned.

In the majority of cases, local conditions are naturally at the basis of abnormalities revealed by the menstrual history. Many general states, however, are suggested by such anomalies, especially in the case of women in whom the menstrual function has previously been normal and who have not reached the age of the menopause. A few such general conditions may be cited, namely, tuberculosis, chlorosis, Graves' disease, myxedema and hypophyseal disorders (acromegaly).

SYMPTOMS WHICH MAY BE NOTED BY THE EXAMINER WHILE HE IS WRITING THE HISTORY AND BEFORE HE HAS BEGUN THE EXAMINATION PROPER

At this point we shall consider, very briefly, certain matters which belong properly in the province of the physical examination and not in a chapter devoted to the writing of histories. However, the author has thought it advisable to risk the criticism of encroaching upon the field of physical diagnosis in order to emphasize the preëminent importance of the education of the physician's sense of observation. Although it is no doubt true that the power to see manifestations in the patient is to some extent a gift not possessed by all, it is equally true that the man who tends to overlook what is obvious to another can educate his undeveloped or neglected sense of observation to no small degree.

Perhaps by this repetition the author can assist in correcting another failing all too common among practitioners, namely, that of resorting at once to palpation, percussion or auscultation, before the eyes have been given a chance to observe.

The following are among the more important points of information (the list is by no means an exhaustive one) which the physician may have been able to gather upon meeting the patient, and during the preparation of the history, before he has begun the actual physical examination.

Mental State.—A very fair idea of the patient's mental condition should have been gained by the time the history has been written, provided, of course, his sensorium is such that he can answer questions. Indeed, the diagnosis of the psychoses and neuroses must, in great part, rest upon what the patient says and his way of saying it, supplemented, if need be, by the statements of relatives and friends.

Insanity, aside from quiescent periods which may be part and parcel of certain types, is usually easily recognized as such. The emotional side of *hysteria* will scarcely be held in complete abeyance while the individual is being questioned. There may be attacks of weeping, crying, laughing, perhaps cries which mimic the sounds produced by animals, as barking, mewling, etc., or even a characteristic convulsive seizure especially staged for the physician. The *neurasthenic* generally betrays himself by his low-spirited and despondent mien, which is apt to be reflected in his mode of approach and even in his dress; while as the recital of the history progresses, his all-embracing symptom-complex, his anxieties, his phobias, etc., confirm what observation alone has suggested. However, the author cannot refrain from digressing to emphasize that if the examiner wishes to avoid serious error he must not make his final diagnosis of *hysteria* or *neurasthenia* until the routine examination has been completed, for it not infrequently happens that one or the other of these conditions is superimposed upon the basis of an organic process.

As regards the patient's *sensorium* we either recognize the individual to be in full control of his mental faculties, or, on the contrary, we note the presence of such deviations from the normal as *coma*, which may be of different degrees, varying from the form in which the patient may easily be aroused to that in which unconsciousness is absolute; *delirium*, which may be quiet, noisy or mixed; or *stupor*, such as results from alcohol or opiates.

Mode of Approach.—Such information as may be derived from observation of the bedridden individual will be discussed below. The ambulatory patient cannot fail to make a very definite impression upon the physician, merely by his mode of approach. An erect carriage and an energetic gait point generally to some illness of a minor nature; a bent figure and a slow, calculated walk, to a serious illness or perhaps to mental depression. An unusual gait may clinch the diagnosis—or a portion of it, at least—at a glance (tabes dorsalis, hip-joint disease, hemiplegia, paralysis agitans, etc.).

Facial Expression.—Data of great diagnostic value may be derived from a close observation of the patient's facial expression. First of all, conclusions as to his mental state (*see* above) are based not only upon the content, mode of recital and coherence of his story, but also in great part upon the impression conveyed to the examiner by the play

of his facial muscles. Intelligence and the varying degrees of lack of intelligence quickly reveal themselves by subtleties of expression. The hysterical grimace or purposeless smile are unmistakable, as are also the depressed mien of the neurasthenic.

The expression conveys also such subjective states as pain, anxiety, agitation, uneasiness and care, and gives one a very fair idea of the severity of the patient's illness. The face is furthermore a good index of the presence of fever, which is recognized by a characteristic luster of the eyes and a redness and turgidity of the skin; while the sick individual may in some cases appear peculiarly animated and in others extremely depressed and dull.

Also characteristic are the distress and anxiety of dyspneic patients, the hunted expression in the more advanced stages of pulmonary tuberculosis, the facies hippocratica of peritonitis, the mask-like face of Parkinson's disease, the risus sardonicus of tetanus, the adenoid facies, the acromegalic face (large features, prognathous jaw), and the absent play of the facial muscles in Bell's palsy.

Position in Bed.—Many diseases may be characteristically indicated by the position assumed by the bed-ridden individual. This is illustrated by the case of the *typhoid* patient, for example. After the nurse has given him his morning care, he will remain until disturbed in the position in which he is left, namely, flat on his back in the middle of the bed. The resemblance of one case of typhoid to another is truly remarkable. The individual with disease of the thoracic organs, on the contrary, generally prefers to lie upon his side. Such a condition may properly be assumed to exist if the patient maintains the lateral posture when the physician enters the sick room and even when he is addressed. If pain dominates the picture, the sick man generally prefers to lie upon the unaffected side, as the weight of the body tends to increase the distress. If, on the contrary, the pulmonary function is limited (in pneumonia, fluid or air causing collapse of one lung), lying upon the involved side is preferable, as the healthy—or relatively healthy—side is unimpeded and can better do the work of both. In some cases, however, in which the pain and restrained breathing are more or less dependent one upon the other, the patient is likely to lie upon the side in which the pathology is located, as the body weight tends to act as a splint and thus limits the painful excursions.

In *cardiac disease* the patient may assume any of several positions, the comfortable one in the particular case being that in which the heart can best work under the disadvantages present.

In the severest grade of dyspnea—*orthopnea*—the patient can find a fair degree of comfort only by assuming the upright position, in a chair or propped up in bed, a position which gives the accessory muscles of respiration the freest play and allows the diaphragm to descend more readily, if fluid is present in the abdomen.

In *meningitis*, owing to muscular rigidity, certain constrained positions are common—opisthotonos, and more frequently, orthotonus. In conditions of peritoneal irritation, one or both thighs may be flexed to

relieve the tension upon the psoas muscles and thus to reduce the intra-abdominal tension—the right thigh in appendicitis, both in diffuse peritonitis. In some abdominal conditions associated with pain—colic, for example—the patient finds the greatest relief by lying upon the abdomen.

Finally, in cases in which the history has made a tentative diagnosis possible, the tendency of the patient to remain in a given position may suggest the localization of the process. In sacular bronchiectasis, for example, one may be reasonably sure that the patient does not choose the position which provokes cough with its attendant large expectoration. In presumptive gastric ulcer we have at least the right to assume that if the left lateral position is the most comfortable one the ulcer is not in the neighborhood of the pylorus, or, if lying upon the abdomen gives the greatest relief, that the ulcer involves the posterior wall of the stomach.

Examples of the diagnostic importance of the patient's position in bed or of certain constrained attitudes might be multiplied almost indefinitely; however, the illustrations cited give a very fair idea of what observation may reveal in this province.

Relation of Appearance and Age.—Almost involuntarily, the examiner tells himself that one individual looks his age, that another looks years younger than his age, and that a third man appears considerably older than his years. The young-looking old man has in all probability taken good care of himself as regards food, tobacco, alcohol, exercise, etc., while the chances are that the old-appearing young man has indulged to excess in certain things recognized to be harmful. Factors causing exceptions to these presumptive diagnoses are previous freedom from illness, or the occurrence of considerable previous illness, respectively, and the tendency of the members of some families to retain a youthful appearance and of others to age prematurely.

State of Nutrition.—Although it is not possible to tell by observation alone whether the patient has *lost moderately* in weight or whether he has *gained* slightly or markedly in weight, it is generally not difficult to determine at a glance that there has been a *considerable loss* of weight. One may see this, perhaps, in the loose fit of the clothes, but more particularly in the shrunk appearance of the face, in the hollows about the face, and in some cases by the looseness of the skin of the face. Once it has been determined that the individual has lost a good deal of weight, the commoner causes of such a state (malignancy, tuberculosis, diabetes mellitus, Graves' disease) are automatically suggested to the examiner.

Some experience also enables the physician to judge whether the patient conforms approximately to the age-height-weight-sex ratio, or whether he varies from this ratio in one direction or the other.

Skin and Mucous Membranes.—Observation may yield considerable information regarding the skin and mucous membranes, even from those parts visible before the patient has prepared himself for examination. The color associated with good health need not be dwelt upon. It must not be supposed, however, because the skin is pale, that the individual

is anemic, for although this is frequently the case, the pallor may be congenital and due to the narrow caliber of the cutaneous vessels. If the condition is distinguishable at the distance at which the physician sits from the patient, and if it is evident that the pallor involves also the lips, the lobes of the ears and the gums, then the diagnosis of anemia is justifiable. The interpretation of generalized abnormal coloring of the skin will of course be obvious—jaundice, cyanosis, pigmentation, etc.

Many diseases of the skin involve characteristically the covering of those parts (face, neck and hands) which are being considered in the visual examination. A few may be cited, such as acne, erythema multiforma, eczema, certain of the syphilids—the corona veneris, for example—herpes simplex, lupus erythematosus, and some of the contagious exanthemata (measles, scarlatina with its circumoral pallor, etc.).

Hair and Nails.—It may perhaps be noted that the *hair* of the head is fine and lustrous, or that it is coarse and dead (as in myxedema). Seborrheic eczema is usually recognized at a glance from the branny scales on the hair, which may be either oily (oily seborrhea) or dry (dry seborrhea). Equally obvious are the alopecias—luetic, alopecia areata, and that most common form which generally defies a search for its cause and therapy. The characteristic lesions of psoriasis also may frequently be seen at the hair-line of the forehead.

The *nails* may also show a great deal. The care bestowed upon these appendages throws a good deal of light upon the habits of the individual. The nails of the worker in lead often strikingly indicate the reason why a particular individual has been poisoned by the metal. Many diseases involving the skin likewise leave their mark upon the nails (eczema, syphilis, psoriasis). Blueness of the nails associated with clubbed fingers will be mentioned in another place.

The Lymph-nodes.—The cervical chains of nodes are the only ones visible as the patient's history is being written, and these must have attained a certain size before they attract attention. Among the characteristic pictures at once suggested to the experienced eye are the collar of glands in Hodgkin's disease, and the enlargements, with fistulæ, of tuberculosis.

Vasomotor Disturbances.—The patient whose hand is shaken in greeting may at once betray the instability of his vasomotor system by his moist grip; or, he may frequently wipe his hands with his handkerchief during the course of the questioning. Another manifestation of this same instability is the flushing, or alternate paling and flushing, seen in the faces of some patients.

Cough and Expectoration.—A very fair presumptive diagnosis can often be made from a close observation of the type of cough or the character of the expectoration of some individuals, if the physician is present at a favorable moment. The brassy cough of aneurism of the aorta or of some other mediastinal tumor, the whoop of pertussis, the hollow, toneless cough of advanced tuberculosis and the productive cough of pulmonary cavities, brought on by a change of position, may be cited as illustrations.

If the patient expectorates during the preparation of the anamnesis, the physician is often enabled to obtain much information from the character of the sputum. One suspects pulmonary softening (abscess, tuberculosis) if a large amount of purulent material is brought up at frequent intervals; bronchiectasis is indicated if the expectoration is a "mouthful"; lobar pneumonia when the sputum is rusty; tuberculosis, or perhaps cardiac disease, when the material is blood-streaked, and gangrene when the never-to-be-mistaken odor is present.

The Breathing.—The orthopnea of decompensated hearts has already been mentioned. Other characteristic types are the dyspnea, with expiratory grunt, of pneumonia, the expiratory difficulty of emphysema, the inspiratory dyspnea, with recourse to the accessory muscles of respiration and fixed position of the spine and arms, in stenosis of the upper air-passages (diphtheria, foreign body), the asthmatic type with its easily-heard wheeze (true bronchial asthma, cardiac and renal disease), the air-hunger of diabetic coma, and the Cheyne-Stokes type of breathing occurring particularly in uremia and in cardiac and intracranial conditions.

The Voice and the Speech.—The severely ill or extremely weak individual generally betrays his condition by his voice; the tonal quality of the latter suffers also in dyspneic states. The "thick" voice of chronic alcoholism, furthermore, is quite distinctive. Ulcerative processes (syphilis, tuberculosis, cancer) involving the cords give to the voice a raucous quality that is unmistakable. Paralysis of the vocal cords produce an aphonia which must at once guide the trend of the examination.

The speech of certain diseases (multiple sclerosis, general paresis and bulbar paralysis) may also be characteristic.

The Eyes.—During the progress of the history writing the physician may observe few or many eye symptoms, depending upon how close he is to the patient, and how favorable the light is. When one or more extrinsic muscles are paralyzed the fact is of course obvious, although the examination proper must determine the details of the paralysis. The same is true of an injection of the visible blood-vessels, i.e., the redness of the eye may be due to conjunctival or to circumcorneal injection, which the later examination must reveal, as well as determining the cause of the injection (foreign body, type of organism, etc.).

Cataract is often recognized at a glance. Inequalities of the pupils of sufficient degree are also frequently evident in a good light. Unilateral or bilateral exophthalmos is, of course, obvious. In addition, mere observation is sufficient to make a diagnosis of a number of diseases of the external eye which need not be enumerated at this point.

The Ears.—Defective hearing in both ears is quickly noted; if, however, only one ear is involved, practice may have made the patient so proficient in concealing the weakness by the use of the sound, or sounder, ear, that the fact may escape the examination by observation.

Observation may also not infrequently reveal the presence of gouty tophi in the ears.

The Teeth.—Information as to the teeth may in some cases be obtained by observation alone, particularly in the case of individuals who have a habit of showing their teeth. Notched incisors, ulcerative conditions of the gums, missing teeth and pyorrhea are among the conditions which may, occasionally be revealed by an examination carried out under the limitations imposed.

The Breath and the Body Odor.—The ordinary bad breath, although frequently evident even at a distance, indicates only one of a number of possible causes. Certain breaths, on the other hand, are highly significant. Of the odor due to the recent drinking of alcohol, nothing need be said. Just as characteristic, although not easy to describe, is the breath of the chronic drinker. The fruity breath of the diabetic, due to acetone, is diagnostic, although it is said that all physicians are not able to appreciate this odor. The frightful odor of pulmonary gangrene baffles description. As another example of a diagnostic breath, finally, may be mentioned that of uremia, which is urinary in character.

Patients with certain diseases are said to give off body odors characteristic of those diseases. Among the latter are typhoid fever, small-pox and syphilis.

The Extremities.—The hands are visible in this examination, and characteristic symptoms or conditions may be observed in certain cases. Clubbed fingers—the broadening of the terminal phalanges with an exaggerated arching and cyanosis of the nail—indicate principally congenital heart disease and bronchiectasis, and less often other cardiac and pulmonary conditions. One may note also the red periarticular swellings of rheumatic fever, the deformed joints of subacute and chronic infectious arthritis, the chalky nodules of gout, Heberden's nodes, the large hand of acromegaly, the changes associated with Raynaud's disease, erythromelalgia and thrombo-angiitis obliterans, the spindle-shaped enlargements of one or more digits due to tuberculosis or to syphilis, and the "claw-hand" of paralysis of the median or ulnar nerve.

The Abdomen.—Observation reveals little regarding the abdomen, except the presence of considerable enlargement, the cause of which must be determined by the examination to follow.

Edema.—As the patient, clothed, sits before the physician, the latter can observe edema of the eyelids, if present, edema of the entire face, swelling of the hands, swelling of the thighs and perhaps of the legs, if very marked, and finally edema of the ankles, if the individual presents himself with loosened shoe-laces.

Visible Nervous Manifestations.—Certain characteristic gaits have already been mentioned (p. 588). *Tremors* of various types may be observed in different localities. This symptom is perhaps most frequent in the hands, and the type of the movement in certain diseases may be very characteristic (paralysis agitans, multiple sclerosis, old age). A trembling of the eyelids is often seen in neurasthenia. Occasionally the patient is first seen at the beginning or during the course of a general convulsion. This may be of the epileptic type (tonic followed by clonic movements), of the tetanic form, as in tetanus, or of the jacksonian type

CASE HISTORY TAKING

in which the convulsive wave, beginning at one point—usually an extremity—progressively involves the entire body.

The large, incoördinated movements of chorea are at once noted, as are athetoid movements of the fingers and the spasm of the hands in tetany. That ominous symptom—subsultus tendinum, i.e., the leaping of the tendons of the back of the hands and wrist—is seen especially in typhoid fever. Habit spasms (tics) most often involve the face, throat and shoulders, although the hands may be affected.

Paralyses can frequently be made out by observation only. It is possible in some cases to say that the patient whose history is being written suffers from hemiplegia (the gait has already been noted), from monoplegia or paraplegia. Or one may observe that the paralysis is flaccid, involving a peripheral neuron, as in poliomyelitis, or spastic, due to a cerebral lesion. The former hypothesis is strengthened if considerable atrophy can be made out, the latter if the atrophy is not prominent.

In the foregoing pages the effort has been made to show how rich the information is which may be derived from observation alone. All of the data contained in these pages can be stored away in the physician's mind during the progress of the history taking and before the examination proper has been started. It may be added that these data are by no means all-inclusive, but are given only as the more important, perhaps, of the signs and symptoms to be gathered under these conditions.

In conclusion, it may be said that with a history taken and analyzed under the conditions discussed above, the examiner should feel that he has built a substantial foundation for his diagnosis.

IMPORTANT

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